IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

SANOFI and SANOFI-AVENTIS U.S. LLC, Plaintiffs, v. GLENMARK PHARMACEUTICALS INC., USA, et al., Defendants.	Civil Action No. 14-264-RGA (CONSOLIDATED)

TRIAL OPINION

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Richard G. Andrews

ANDREWS, U.S. DISTRICT JUDGE:

Plaintiffs Sanofi and Sanofi-Aventis U.S. LLC (collectively, "Sanofi") brought suits against eight generic Defendants alleging infringement of U.S. Patent Nos. 8,318,800 ("the '800 patent"), 8,410,167 ("the '167 patent"), and 8,602,215 ("the '215 patent"), including Defendants Watson Laboratories, Inc., Watson Pharma, Inc., and Actavis, Inc. (collectively, "Watson") (C.A. No. 14-265-RGA, D.I. 1) and Defendant Sandoz Inc. (C.A. No. 14-1434-RGA, D.I. 1). Sanofi's related infringement actions against the various defendants were consolidated for all purposes with *Sanofi et al. v. Glenmark Pharmaceuticals Inc., USA, et al.*, C.A. No. 14-264-RGA.[1] (C.A. No. 14-265-RGA, D.I. 24 at 3; C.A. No. 14-1434, D.I. 14). Sanofi's claims against Glenmark and all the other generic defendants were resolved via stipulations prior to trial. The '215 patent is also no longer at issue. The Court held a three-day bench trial on Sanofi's claims against Watson and Sandoz, related to issues of infringement and invalidity pertaining to the '167 patent, from June 7–9, 2016. (D.I. 326, 327, 328, 329).[2] The parties filed post-trial briefing, which also included arguments on an outstanding issue of claim construction applicable to the '800 patent. (D.I. 299, 300, 305, 306, 309, 310). Having considered the documentary evidence and testimony, the Court makes the following findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a).

I. BACKGROUND

A. Overview

Plaintiff Sanofi-Aventis U.S. LLC is the holder of approved New Drug Application ("NDA") No. 022425 for 400 mg dronedarone tablets, which are prescribed and sold in the

[1] All citations to the docket will be to C.A. No. 14-264-RGA, unless otherwise noted.

[2] Although the official transcript is filed in four parts (D.I. 326, 327, 328, 329), citations to the transcript herein are generally cited only as "Tr."

United States under the trademark Multaq®. (D.I. 1 at ¶ 19). "Multaq® is an antiarrhythmic drug indicated to reduce the risk of hospitalization for atrial fibrillation (AF) in patients in sinus rhythm with a history of paroxysmal or persistent AF." (JTX 192 at 1). "Dronedarone [hydrochloride] is a benzofuran derivative" that "has antiarrhythmic properties belonging to all four Vaughan-Williams classes, but the contribution of each of these activities to the clinical effect is unknown." (JTX 192 at 11).

The '800 patent claims pharmaceutical compositions containing dronedarone and is listed in the FDA's Orange Book for Multaq® tablets (NDA No. 022425). (D.I. 1 at ¶ 20). The '167 patent claims methods of decreasing the risk of cardiovascular hospitalization and hospitalization for atrial fibrillation in a specific class of patients, and is also listed in the FDA's Orange Book for Multaq® tablets. (*Id.* at ¶ 22). Watson and Sandoz each filed Abbreviated New Drug Applications ("ANDAs") seeking FDA approval to market generic versions of Multaq®. Watson seeks approval through ANDA No. 205682. (C.A. No. 14-265-RGA, D.I. 1 at ¶ 30). Sandoz seeks approval through ANDA No. 205744. (C.A. No. 14-1434-RGA, D.I. 1 at ¶24). Watson's ANDA and Sandoz's ANDA contain Paragraph IV certifications alleging that both the '800 and '167 patents are invalid and/or will not be infringed by the manufacture, use, or sale of their proposed generic products. (C.A. No. 14-265-RGA, D.I. 1 at ¶ 34; C.A. No. 14-1434-RGA, D.I. 1 at ¶ 27). Sanofi received notices of Watson and Sandoz's Paragraph IV certifications and initiated the present lawsuits, which were later consolidated.

Atrial fibrillation ("AF"), which dronedarone is designed to treat, is the most common heart rhythm disorder and is characterized by an irregular, rapid heartbeat from the atrium, the upper chamber of the heart. (Tr. 64:6–12). In AF, the electrical signals that are normally generated regularly by the sinus node, which keep the heart beating in a coordinated fashion,

become disorganized, leading to "the disordered contraction of the atria followed by the regularly irregular [pumping] response of the ventricles." (Tr. 158:13–160:4). There are generally three types of AF. Paroxysmal AF occurs for short periods of time and the heart is generally able to return to normal sinus rhythm without medical intervention. (Tr. 160:7–11). Persistent AF lasts for a longer period of time, usually a week or more, and often requires medical intervention, such as electrical cardioversion or drug therapy, in order to restore normal sinus rhythm. (Tr. 65:9–12, 160:12–17). Permanent AF occurs when patients cannot be returned to normal sinus rhythm, even after drug therapy or attempts at electrical cardioversion. (Tr. 65:12–16, 160:18–23). One strategy that medical professionals use to treat AF is called "rhythm control" and involves the administration of antiarrhythmic drugs ("AADs"), a class of drugs designed to maintain the heart's normal sinus rhythm. (Tr. 67:15–23). Dronedarone, the pharmaceutical compound at issue in this suit, is an AAD. (Tr. 67:21–23).

II. '167 PATENT

The '167 patent claims methods of reducing the risk of cardiovascular hospitalization by administering the drug dronedarone to a class of patients who have at least one of six specific cardiovascular risk factors. (JTX 3). Sanofi asserts that Defendants' proposed labels for their generic dronedarone products will induce and contribute to infringement of claims 1–6, 8–13, and 16 of the '167 patent. There are two independent claims, 1 and 8. Claims 2–6, and 9–12 depend from Claim 1. Claims 13 and 16 depend from claim 8. Claim 1 reads as follows:

> 1. A method of decreasing a risk of cardiovascular hospitalization in a patient, said method comprising administering to said patient an effective amount of dronedarone or a pharmaceutically acceptable salt thereof, twice a day with a morning and an evening meal, wherein said patient does not have severe heart failure, (i) wherein severe heart failure is indicated by: a) NYHA Class IV heart failure or b) hospitalization for heart failure within the last month; and (ii) wherein said patient has a history of, or current, paroxysmal or persistent non-permanent

> atrial fibrillation or flutter, and (iii) wherein the patient has at least one cardiovascular risk factor selected from the group consisting of:
> i. an age greater than or equal to 75;
> ii. hypertension;
> iii. diabetes;
> iv. a history of cerebral strokes or of systemic embolism;
> v. a left atrial diameter greater than or equal to 50 mm; and
> vi. a left ventricular ejection fraction less than 40%.

('167 patent, claim 1). Independent claim 8 is nearly identical to independent claim 1, aside from specifying a decrease in the risk of "hospitalization for atrial fibrillation" instead of "cardiovascular hospitalization." (*Id.*, claim 8). Specific aspects of claims 4, 5, and 10 are also implicated by the parties' arguments. Those claims read as follows:

> 4. The method according to claim 1, wherein said patient further receives a diuretic-based treatment.
>
> 5. The method according to claim 4, wherein said diuretic is a non-potassium-sparing diuretic.
>
> 10. The method of claim 1, wherein the administration of said effective amount is maintained for at least 12 months.

(*Id.* claims 4, 5, 10).

Sanofi's definition of the POSA with respect to the '167 patent is "a clinician with a medical degree who was board certified either in cardiology or electrophysiology that has at least two years of clinical experience after fellowship and because of such fellowship would have some knowledge of the design, implementation, and analysis of clinical studies." (Tr. 83:9–16, 537:3–7). Defendants' definition of the POSA with regard to the '167 patent is a person with a "medical degree and experience treating patients with cardiovascular disorders as a cardiologist or general practitioner or a person with a degree or advanced degree in pharmacology with at least five years of clinical experience." (Tr. 174:7–15). The Court will adopt Sanofi's definition of a POSA, as it better captures the specialists that would likely be prescribing dronedarone to an

at-risk, older patient suffering from paroxysmal or persistent AF, in accordance with the claims of the '167 patent. I also think that a POSA, in considering whether a not-yet-approved drug could successfully treat certain conditions, would have at least some understanding of the design, implementation, and analysis of clinical trials. In any event, the parties' respective experts on infringement and invalidity all indicated that their conclusions would not be affected by the definition of the POSA ultimately adopted by the Court. (Tr. 84:16–19, 175:8–12).

With regard to the effective filing date of the '167 patent, Defendants argue that Sanofi is not entitled to a priority date before February 11, 2009, because provisional applications before that date did not disclose every element of independent claims 1 and 8. (D.I. 300 at p. 3 (citing JTX 37; JTX 38; Tr. 430:19–434:21 (testimony of Davide Radzik))). Sanofi does not contest this characterization, nor does it appear it has grounds to. Recognizing this priority date and that Defendants' principal obviousness references are from 2008 or earlier, both parties direct their arguments to what a POSA would understand as of 2008 for ease of reference. The Court will do so as well throughout this Opinion.

A. Infringement

1. Legal Standards

A patent is infringed when a person "without authority makes, uses, offers to sell, or sells any patented invention, within the United States . . . during the term of the patent . . . ." 35 U.S.C. § 271(a). A two-step analysis is employed in making an infringement determination. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). First, the court must construe the asserted claims to ascertain their meaning and scope. *See id.* The trier of fact must then compare the properly construed claims with the accused infringing product. *See id.* This second step is a question of fact. *Bai v. L & L Wings,*

Inc., 160 F.3d 1350, 1353 (Fed. Cir. 1998). "Literal infringement of a claim exists when every limitation recited in the claim is found in the accused device." *Kahn v. Gen. Motors Corp.*, 135 F.3d 1472, 1477 (Fed. Cir. 1998). "If any claim limitation is absent from the accused device, there is no literal infringement as a matter of law." *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1247 (Fed. Cir. 2000). The patent owner has the burden of proving infringement by a preponderance of the evidence. *See SmithKline Diagnostics, Inc. v. Helena Labs. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988).

35 U.S.C. § 271(b) provides that "[w]hoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b). "In order to prevail on an inducement claim, the patentee must establish first that there has been direct infringement, and second that the alleged infringer knowingly induced infringement and possessed specific intent to encourage another's infringement." *ACCO Brands, Inc. v. ABA Locks Mfrs. Co.*, 501 F.3d 1307, 1312 (Fed. Cir. 2007) (internal quotation marks omitted). In other words, "inducement requires evidence of culpable conduct, directed to encouraging another's infringement, not merely that the inducer had knowledge of the direct infringer's activities." *DSU Med. Corp. v. JMS Co.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006) (en banc). "[S]pecific intent may be inferred from circumstantial evidence where a defendant has both knowledge of the patent and specific intent to cause the acts constituting infringement." *Ricoh Co. v. Quanta Computer Inc.*, 550 F.3d 1325, 1342 (Fed. Cir. 2008). "[L]iability for induced infringement can only attach if the defendant knew of the patent and knew as well that 'the induced acts constitute patent infringement.'" *Commil USA, LLC v. Cisco Sys., Inc.*, 135 S. Ct. 1920, 1926 (2015) (quoting *Global–Tech Appliances, Inc. v. SEB S.A.*, 131 S. Ct. 2060, 2068 (2011)). The knowledge requirement may be satisfied by showing actual knowledge or willful blindness. *See Global–Tech,* 131 S. Ct. at 2068 (2011).

In Hatch-Waxman cases alleging that a proposed drug label will induce infringement by physicians, "The pertinent question is whether the proposed label instructs users to perform the patented method." *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010). "The label must encourage, recommend, or promote infringement." *Takeda Pharm. USA, Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015). "The mere existence of direct infringement by physicians, while necessary to find liability for induced infringement, is not sufficient for inducement." *Id.* Rather, "specific intent and action to induce infringement must be proven." *Id.* (internal quotation marks omitted). Even where a proposed label does not explicitly track the language of a claimed method, a package insert containing directives that will "inevitably lead some consumers to practice the claimed method" provides sufficient evidence for a finding of specific intent. *See AstraZeneca*, 633 F.3d at 1060; *see also Abraxis Bioscience, Inc. v. Navinta, LLC*, 630 F. Supp. 2d 553, 570 (D.N.J. 2009) ("Statements in a package insert that encourage infringing use of a drug product are alone sufficient to establish intent to encourage direct infringement."), *rev'd and vacated on other grounds*, 625 F.3d 1359 (Fed. Cir. 2010).

With regard to contributory infringement, 35 U.S.C. § 271(c) provides:

> Whoever offers to sell or sells within the United States or imports into the United States a component of a patented machine, manufacture, combination or composition, or a material or apparatus for use in practicing a patented process, constituting a material part of the invention, knowing the same to be especially made or especially adapted for use in an infringement of such patent, and not a staple article or commodity of commerce suitable for substantial noninfringing use, shall be liable as a contributory infringer.

To establish contributory infringement, the plaintiff must prove: "1) that there is direct infringement, 2) that the accused infringer had knowledge of the patent, 3) that the component has no substantial noninfringing uses, and 4) that the component is a material part of the

invention." *Fujitsu Ltd. v. Netgear Inc.*, 620 F.3d 1321, 1326 (Fed. Cir. 2010). This provision "reflect[s] patent law's traditional staple of commerce doctrine . . . that distribution of a component of a patented device will not violate the patent if it is suitable for use in other ways." *Metro-Goldwyn-Mayer Studios Inc. v. Grokster, Ltd.*, 545 U.S. 913, 932 (2005). "In sum, where an article is good for nothing else but infringement, there is no legitimate public interest in its unlicensed availability, and there is no injustice in presuming or imputing an intent to infringe." *Id.* (citations and internal quotation marks omitted).

2. Findings of Fact

1. A physician would look to the indications and usage section of Defendants' proposed labels to see if their proposed ANDA product is specifically indicated for administration to patients with certain characteristics. The indications and usage section of Defendants' proposed labels states that "dronedarone tablets are indicated to reduce the risk of hospitalization for atrial fibrillation in patients in sinus rhythm with a history of paroxysmal or persistent atrial fibrillation (AF) *[see Clinical Studies (14)]*." A physician would follow that directive and review section 14 of the labels, the clinical studies section.

2. When reviewing the clinical studies section, a physician would first find section 14.1, describing the ATHENA clinical trial. The physician would read that in the ATHENA trial, "Dronedarone reduced the combined endpoint of cardiovascular hospitalization or death from any cause by 24.2% when compared to placebo. This difference was entirely attributable to its effect on cardiovascular hospitalization, principally hospitalization related to AF." The physician would continue reading the clinical studies section of the proposed labels, and find that the descriptions of the other clinical studies do not mention anything about reducing cardiovascular hospitalizations or hospitalizations for AF.

3. The "Clinical Studies" section of Defendants' proposed labels provides a description of the patients involved in the ATHENA clinical trial. The labels state that the ATHENA trial involved patients that were at least 75 years old, or were at least 70 years old with at least one cardiovascular risk factor from a list including hypertension, diabetes, prior cerebrovascular accident, left atrial diameter greater than or equal to 50 mm, or left ventricular ejection fraction less than 40%. These are the identical risk factors listed in claims 1 and 8 of the '167 patent. The physician would thus recognize that the only patient group in which the indicated use has been proven successful is the ATHENA patient population, which involved patients with at least one of the associated risk factors.

4. Defendants had knowledge of the '167 patent.

5. Approximately 77% of Multaq® prescriptions are made to patients having at least one of the claimed cardiovascular risk factors. The label for Multaq® is identical to Defendants' proposed labels.

6. Diuretics are commonly used to treat cardiovascular conditions such as hypertension and heart failure. Defendants' proposed labels state that 54% of ATHENA patients were also being treated with diuretics while taking dronedarone.

7. Defendants' proposed labels warn that hypokalemia or hypomagnesemia may occur with concomitant administration of dronedarone and potassium-depleting diuretics.

8. AF is a chronic disorder and physicians generally intend to maintain AF treatments indefinitely. Defendants' proposed labels state that the median treatment time during the ATHENA trial was 22 months.

3. Conclusions of Law

Defendants raise three principal non-infringement arguments. First, with regard to inducement, Defendants argue that their proposed labels do not instruct only administering dronedarone to patients having one of the claimed risk factors. (D.I. 305 at pp. 8–15). Second, Defendants contend that their labels do not instruct using dronedarone with diuretics (claims 4 and 5) or for at least twelve months (claim 10). (*Id.* at pp. 15–16). Third, Defendants argue that Sanofi has failed to prove contributory infringement of the '167 patent because Defendants' proposed ANDA products are capable of substantial, non-infringing uses. (*Id.* at pp. 16–18).

a. Inducement to Treat Patients with Risk Factors (all claims)

Defendants' principal non-infringement argument is that their proposed labels do not evidence specific intent to instruct or encourage administration of dronedarone to patients with specific cardiovascular risk factors, as expressly required by independent claims 1 and 8 of the '167 patent and in turn by all of the asserted dependent claims. Sanofi argues that Defendants' labels, which copy Sanofi's label for Multaq®, encourage the use of dronedarone in patients having at least one of the claimed cardiovascular risk factors. (D.I. 299 at p. 3). Sanofi argues, citing testimony of Defendants' expert Dr. Randall Zusman, that it is undisputed that a POSA

presented with Defendants' labels would look to, among other sections, the indications and usage section of the label. (*Id.* at p. 4; Tr. at 180:12–181:12). Sanofi then points out that the indications and usage sections of Defendants' labels state, "Dronedarone tablets are indicated to reduce the risk of hospitalization for atrial fibrillation in patients in sinus rhythm with a history of paroxysmal or persistent atrial fibrillation," and direct the reader to look at the clinical studies section. (D.I. 299 at p. 4; JTX 257 at 494 (Watson); PTX 229 at 311 (Sandoz)).[3] Sanofi contends that once a POSA looked to the clinical studies section, the POSA would first be presented with a description of the ATHENA clinical trial. (D.I. 299 at pp. 4–5).

According to Sanofi, and its infringement expert Dr. Michael H. Kim, this description of the ATHENA trial would show three things. First, they point out that it is the only clinical trial disclosed in the label that demonstrates dronedarone's ability to reduce the risk of cardiovascular hospitalization and hospitalization for AF. (D.I. 299 at p. 5; Tr. at 71:5–22, 109:18–110:14). Second, they contend that a POSA would recognize that the patient population in the ATHENA trial, consistent with the claims of the '167 patent, all "had a recent history of non-permanent atrial fibrillation or flutter and were at least 75 years of age or 70 years of age with at least one cardiovascular risk factor." (D.I. 299 at p. 5; Tr. 91:20–92:22). Third, they assert that a POSA would recognize that ATHENA was the first study in which any AAD demonstrated an ability to reduce the risk of cardiovascular hospitalization, despite numerous past dronedarone studies having taken place involving different patient populations. (D.I. 299 at p. 5; Tr. at 96:5–8).

Defendants argue that their proposed labels do not evidence the specific intent to instruct or encourage administration of dronedarone only to patients with risk factors. Defendants cite

[3] Because Defendants acknowledge that both of their proposed labels (JTX 257 and PTX 229) are identical, the Court will only cite to Watson's proposed label (JTX 257) hereinafter, for the sake of simplicity. Likewise, citations to specific pages of the Watson label will be limited to the last three digits of the Bates numbers appearing therein.

the original Multaq® label, which included in its indications and usage section an express reference to the risk factors of the ATHENA population, as evidence that the modified Multaq® label, which Defendants' copied, fails to comparably highlight the risk factors. (D.I. 305 at p. 2; DTX 323 at 157). Defendants further point to various sections of their labels, such as warnings and contraindications, which make no mention of administering the drug only to patients with risk factors. (D.I. 305 at p. 3). Defendants emphasize that the reference to the clinical studies section within the indications and usage section does not specifically reference the ATHENA trial, but instead directs the reader to all of section 14, which describes the results from five different clinical trials. (*Id.* at pp. 3–4, 13; JTX 257 at 494, 508–12). In particular, Defendants highlight the summary of the EURIDIS and ADONIS ("E/A") trials in section 14, arguing that this section "informs doctors and patients that dronedarone benefits patients who do not have a Risk Factor," by delaying the time to first recurrence of AF and lowering the risk of first AF recurrence. (D.I. 305 at p. 4; JTX 257 at 511–12).

Defendants also maintain that "[t]he actual prescribing practices of physicians further confirm that the labels do not restrict the use of dronedarone to patients with a Risk Factor." (D.I. 305 at p. 4). They point to "[a]n epidemiology study conducted by Sanofi [that] showed that at least 23% of the patients who are prescribed Multaq® do not have a Risk Factor." (*Id.*; Tr. 102:9–103:20 (Dr. Kim); Tr. 195:6–197:12 (Dr. Zusman)). Defendants also note that both parties' experts admitted that between 15% and 20% of the patients to whom they prescribe dronedarone do not have a risk factor. (D.I. 306 at p. 4; Tr. 98:8–24, 102:2–103:20 (Dr. Kim); Tr. 194:24–195:5 (Dr. Zusman)). Defendants also cite various Sanofi marketing materials that advertise the benefits described in the E/A trials. (D.I. 305 at p. 5). Defendants thus assert that their labels "are indifferent to whether dronedarone is to be administered to patients with a Risk

Factor" because they do not explicitly instruct administration to patients with a risk factor and cite the entire clinical studies section, which lists other uses. (*Id.* at p. 8).

Defendants maintain that Sanofi presented insufficient evidence from which to infer specific intent to encourage infringement. (*Id.* at p. 12). First, they argue that because their products have substantial non-infringing uses, intent to induce infringement cannot be inferred. (*Id.*). Second, Defendants contend that, in the absence of explicit instructions to administer dronedarone to patients with risk factors, "Sanofi tries to construct a series of inferences in Defendants' labels to try to prove intent." (*Id.* at pp. 12–13). Defendants rely on *Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317 (Fed. Cir. 2009) and *United Therapeutics Corp v. Sandoz, Inc.*, 2014 WL 4259153 (D.N.J. June 23, 2014), as allegedly comparable cases "demonstrat[ing] that Defendants do not possess the necessary specific intent to induce infringement of any asserted claim of the '167 patent." (*Id.* at pp. 13–15).

Sanofi responds by asserting that Defendants' non-infringement argument as to the risk factors rests on the improper legal position "that the only scenario that Plaintiffs could prove intent to induce would be a circumstance where [the] product labels explicitly state that their generic products can only be used in patients that fall within the scope of the asserted claims." (D.I. 299 at p. 11). Sanofi relies on *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042 (Fed. Cir. 2010) as standing for the principle that a finding of inducement does not require explicit instructions tracking the exact language of the patent's claims, where the label otherwise sufficiently encourages an infringing use. (*Id.* at pp. 11–12). Thus, Sanofi maintains that "while Defendants' product labels do not explicitly state that dronedarone is only to be used in patients with one of the claimed risk factors, there can be no doubt that Defendants' product labels will encourage the administration of dronedarone to at least some patients with cardiovascular risk

factors specifically to decrease risk of cardiovascular hospitalization in accordance with the claims." (*Id.* at p. 12).

I find that Defendants' proposed labels encourage physicians to prescribe dronedarone to patients with at least one of the cardiovascular risk factors claimed in the '167 patent. In fact, Sanofi's identical label for Multaq® has already encouraged such use, demonstrated by the fact that at least 77% of patients who are prescribed Multaq® have at least one of the claimed cardiovascular risk factors. Moreover, I find that Sanofi has proven by a preponderance of the evidence that Defendants knew that their proposed labels would actually cause physicians to prescribe dronedarone to patients with the cardiovascular risk factors claimed in the '167 patent, and that Defendants knew that such a use would infringe the '167 patent. Because Sanofi has proven that Defendants' proposed labels demonstrate specific intent to encourage physicians to infringe independent claims 1 and 8 of the '167 patent and will lead to such infringement, I conclude that Defendants induce infringement of claims 1 and 8 of the '167 patent. *See Takeda Pharm. USA, Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015).

Sanofi's expert on infringement, Dr. Michael H. Kim, testified that the layout of Defendants' labels, particularly the section describing the ATHENA clinical trial, demonstrates "a clear encouragement of the use of Dronedarone in patients with cardiovascular risk factors in accordance with Claim 1 of the '167 patent." (Tr. 91:20–93:1). Dr. Kim testified that it was important to include information from the other clinical trials to highlight the safety concerns with administering dronedarone to specific patient populations—those of the PALLAS and ANDROMEDA studies—and to compare those concerns with the modest benefits of dronedarone shown in the E/A studies. (Tr. 94:3–97:6). Dr. Kim further testified that a POSA would read Defendants' labels and understand that the FDA-approved used of dronedarone arose

out of the ATHENA trial, which involved patients with at least one of the claimed cardiovascular risk factors. (Tr. 110:1–14). He also testified that a POSA would read the labels with the understanding that past studies involving AADs—such as the CAST and AFFIRM studies—showed either negligible benefits or even adverse consequences from taking dronedarone, such as increased mortality. (Tr. 74:16–78:23).

Dr. Zusman testified that because the indications and usage section, contraindications section, and warnings and precautions section in Defendants' labels all do not expressly limit the use of dronedarone to patients with risk factors, a POSA would not read the labels as encouraging the use of dronedarone in patients with the claimed cardiovascular risk factors. (Tr. 182:13–187:8). He further testified that the clinical studies section of a drug label "is not designed to instruct physicians to prescribe the drug to any particular patient population." (Tr. 187:19–188:1). However, the question asked of and answered by Dr. Zusman is significant; he concluded that there is nothing in Defendants' labels that "directs doctors to prescribe *only* to patients with the claimed risk factors" or "promotes the use of Dronedarone *only* in patients with the claimed risks factors[.]" (Tr. 192:8–15 (emphases added)). He describes as significant the fact that the labels also describe the positive results of the E/A trials, studies that did not require patients to have a risk factor. (Tr. 192:1–7). Accordingly, Dr. Zusman concluded that, because independent claim 8 and all of the dependent claims include the "at least one cardiovascular risk factor" limitation included in claim 1, Defendants' labels do not induce infringement of any claims in the '167 patent. (Tr. 192:16–193:5). However, Dr. Zusman admitted that a POSA looks to drug labels, in part, "for information about the use of the drug in special or specific populations," and that it is important for the POSA to look at the label's indications section to see if a drug "is indicated for administration to patients of certain characteristics with a certain

intent." (Tr. 180:12–181:12). Dr. Zusman further admitted that the patient population from the ATHENA trial, described in Defendants' labels, is the same patient population described in the claims of the '167 patent, that is, a population suffering from paroxysmal or persistent AF and having at least one of six listed cardiovascular risk factors. (Tr. 169:1–17, 173:1–19).

In their first section, entitled "Indications and Usage," Defendants' labels state, "Dronedarone tablets are indicated to reduce the risk of hospitalization for atrial fibrillation in patients in sinus rhythm with a history of paroxysmal or persistent atrial fibrillation (AF) *[see Clinical Studies (14)]*." (JTX 257 at 494). If the reader follows these instructions and looks at the clinical studies section (14), this section begins with a description of the ATHENA clinical trial, which takes up nearly four pages of each label. (*Id.* at 508–11). The ATHENA section explains, "The objective of the study was to determine whether dronedarone could delay death from any cause or hospitalization for cardiovascular reasons." (*Id.* at 508). It then describes the patient population for the ATHENA trial as those having the same risk factors described in the claims of the '167 patent:

> Initially patients were to be ≥70 years old, or <70 years old with at least one risk factor (including hypertension, diabetes, prior cerebrovascular accident, left atrial diameter ≥50 mm or LVEF<0.40). The inclusion criteria were later changed such that patients were to be ≥75 years old, or ≥70 years old with at least one risk factor. Patients had to have both AF/AFL and sinus rhythm documented within the previous 6 months.

(*Id.*). The ATHENA section then reiterates that "[t]he primary endpoint of the study was the time to first hospitalization for cardiovascular reasons or death from any cause." (*Id.* at 509). It then reports the results: "Dronedarone reduced the combined endpoint of cardiovascular hospitalization or death from any cause by 24.2% when compared to placebo. This difference was entirely attributable to its effect on cardiovascular hospitalization, principally hospitalization related to AF." (*Id.*). Thus, the indications and usage section in Defendants' label directs a

physician to look at the clinical studies section, which describes the results of ATHENA, a clinical trial performed on a patient population with the claimed risk factors and that demonstrated the clinical benefit listed in the indications section. (*Id.* at 494, 508–09).

Although descriptions of multiple clinical trials appear in Section 14, ATHENA's description is prominently placed first and is by far the lengthiest. Significantly, it is the only clinical trial listed which mentions results even remotely matching the indicated use: "reduc[ing] the risk of hospitalization for atrial fibrillation (AF) in patients in sinus rhythm with a history of paroxysmal or persistent AF." (JTX 257 at 494).

Section 14.2 of the labels, covering the E/A trials and upon which Defendants rely heavily, does not mention reduction in the risk of cardiovascular hospitalization or hospitalization for AF. (*Id.* at 511–12). This section merely explains that in a study that involved patients in sinus rhythm with a prior episode of AF or AFL, "dronedarone delayed the time to first recurrence of AF/AFL (primary endpoint), lowered the risk of first AF/AFL recurrence during the 12-month study period by about 25%, with an absolute difference in recurrence rate of about 11% at 12 months." (*Id.* at 512).

Section 14.3, describing the ANDROMEDA trial, explains that a trial involving a sicker population than ATHENA or E/A "was terminated [after 63 days] because of excess mortality in the dronedarone group." (*Id.*).

Section 14.4 rounds out the clinical studies section of the labels by describing the PALLAS study, a study of patients with permanent AF that was terminated early because of a significant increase in mortality, stroke, and hospitalization for heart failure in dronedarone takers compared to the placebo. (*Id.*).

While the sections describing each clinical trial all provide relevant information about the safety and efficacy of administering dronedarone to various patient populations, only the description of the ATHENA trial mentions the indicated use, a reduction in the risk of hospitalization for AF. The description of the ATHENA patient population undisputedly describes a patient population with at least one of the six risk factors claimed in the '167 patent. (Tr. 92:4–19 (Dr. Kim); Tr. 169:4–17, 173:1–19 (Dr. Zusman)).

Based on the labels and testimony of the experts, I find that the labels provide "a clear encouragement of the use of Dronedarone in patients with cardiovascular risk factors in accordance with Claim 1 of the '167 patent." (Tr. at 91:20–93:1). This analysis also applies to the identical cardiovascular risk factors appearing in independent claim 8.[4] Moreover, I reach this conclusion notwithstanding that I agree with Dr. Zusman that Defendants' labels, as written, do not instruct physicians only to administer dronedarone to patients with cardiovascular risk factors. Defendants' arguments relying on this testimony rest on the erroneous legal position that a label cannot induce the administration of dronedarone to patients with risk factors unless the label affirmatively states that dronedarone should only be administered to such patients and not to any other groups of patients. However, the law does not require that a label expressly limit a drug only to a specific use in order to induce infringement of a method of treatment claim. The label must merely "encourage, recommend, or promote" an infringing use. *Takeda Pharm. USA, Inc. v. West-Ward Pharm Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015). In other words, it is

[4] Defendants do not attempt to differentiate meaningfully between independent claims 1 and 8 in arguing that the labels do not evidence specific intent to cause physicians to prescribe dronedarone to patients with risk factors. Indeed, as they appear to implicitly concede, there appears to be little reason to separate the analyses, because the ATHENA section of Defendants' proposed labels states that the 24.2% reduction in the combined endpoint of cardiovascular hospitalization or death from any cause shown in the ATHENA trial "was entirely attributable to its effect on cardiovascular hospitalization, principally hospitalization related to AF." (JTX 257 at 509). Accordingly, the same analysis discussed throughout with regard to claim 1 applies to claim 8, and I likewise conclude that Defendants' proposed labels encourage infringement of independent claim 8 of the '167 patent.

sufficient that Defendants' labels will encourage some physicians to prescribe dronedarone to patients with risk factors and will thus inevitably lead to infringing uses. *See AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010) ("Even if [Defendant] were correct that the [language in the label] may be applied to other dosing regimens, the language . . . would inevitably lead some consumers to practice the claimed method.").

Furthermore, I find that Sanofi has proven by a preponderance of the evidence that Defendants knew that using these labels would cause physicians to prescribe dronedarone to patients with the claimed cardiovascular risk factors, and that such a use would constitute infringement of the '167 patent. *See Commil USA, LLC v. Cisco Sys., Inc.*, 135 S. Ct. 1920, 1926 (2015); *Global–Tech Appliances, Inc. v. SEB S.A.*, 131 S. Ct. 2060, 2068 (2011). Defendants' labels make clear that the reduction in the risk of hospitalization for AF, the only indicated use of dronedarone, has only been proven successful in patients with at least one of the cardiovascular risk factors claimed in the '167 patent. In light of the history of clinical studies on dronedarone described in the labels, including several studies being shut down early due to increased mortality, the fact that the labels mention dronedarone's modest efficacy in delaying the time to first AF/AFL recurrence does not change the fact that the labels showcase the use of dronedarone arising out of the ATHENA clinical trial, which involved a patient population with the claimed risk factors.

Statistics before the Court on the real world use of Multaq® provide additional pieces of persuasive evidence that the identical generic labels not only specifically intend to encourage physicians to prescribe dronedarone to a patient population with the claimed risk factors, but also will actually succeed in doing so. *See, e.g.*, *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1365 (Fed. Cir. 2003) (finding evidence of actual use relevant and concluding that

"[w]here there are many uses for a product . . . and fewer than 1 in 46 sales of that product are for infringing uses, we are not in a position to infer or not infer intent on the part of [Defendant] without any direct evidence."); *Acorda Therapeutics Inc. v. Apotex Inc.*, 2011 WL 4074116, at *19 (D.N.J. Sept. 6, 2011), *aff'd*, 476 F. App'x 746 (Fed. Cir. 2012) (finding statistics on actual usage relevant to inquiry into whether a label evidenced specific intent to induce infringement). A Sanofi internal epidemiology report, dated December 2, 2014, shows that in one database 77.0% of actual dronedarone users had at least one cardiovascular risk factor and that in a second database 72.3% of users had at least one risk factor. (DTX 110 at 26). Dr. Kim testified that approximately 85% of the patients to whom he has prescribed dronedarone have at least one of the claimed cardiovascular risk factors. (Tr. 102:2–8). Similarly, Defendants' expert Dr. Zusman testified that 80% of the patients to whom he has prescribed dronedarone have at least one of the claimed risk factors. (Tr. 195:1–5). I find this to be persuasive evidence that Defendants know that the Multaq® label, and Defendants' identical proposed labels, encourage and actually cause the administration of dronedarone to patients with the claimed cardiovascular risk factors. *See Global–Tech,* 131 S. Ct. at 2068. Likewise, that Defendants' know of the '167 patent is not in dispute and is plainly demonstrated by their filing of Paragraph IV certifications stating that the '167 patent is invalid or not infringed by their proposed ANDA products. Lastly, I find that Defendants know that the uses encouraged by their label constitute infringement of the '167 patent, as the ATHENA sections of their labels describe patients with the exact cardiovascular risk factors claimed in the '167 patent. (Tr. 92:4–19; Tr. 169:4–17, 173:1–19). *See Commil*, 135 S. Ct. at 1926.

Lastly, the cases relied upon by Defendants—*Vita-Mix Corp v. Basic Holding, Inc.*, 581 F.3d 1317 (Fed. Cir. 2009), *Takeda Pharm. USA, Inc. v. West-Ward Pharm. Corp.*, 785 F.3d 625

(Fed. Cir. 2015), and *United Therapeutics Corp. v. Sandoz, Inc.*, 2014 WL 4259153 (D.N.J. June 23, 2014)—are readily distinguishable from the present circumstances. In *Vita-Mix*, a non ANDA case, the defendant altered its product instructions to avoid infringing the plaintiff's method patent after the plaintiff articulated its infringement allegations, but before suit was filed. *Vita-Mix*, 581 F.3d at 1328–29. The Court concluded, "The amended product instructions teach an undisputedly non-infringing use, evidencing intent to discourage infringement. Thus, [Defendant's] product instructions provide no basis on which [Plaintiff] can rely to infer specific intent to encourage infringement." *Id.* at 1329. In *Takeda*, the plaintiff argued that the defendant's label, "though only indicated for prophylaxis of gout," induced infringement of a method patent for treating gout flares "by stating that '[i]f you have a gout flare while taking Mitigare, tell your healthcare provider.'" *Takeda*, 785 F.3d at 632. The plaintiff argued that this instruction would "'inevitably' lead to physicians who are consulted to advise patients taking Mitigare for prophylaxis to simply increase their dose of Mitigare to treat acute gout flares, and that [Defendant] was aware of or willfully blind to this possibility." *Id.* The Federal Circuit emphasized that the plaintiff asked it "to look outside the label to understand the alleged implicit encouragement in the label" and held that this "vague label language cannot be combined with speculation about how physicians may act to find inducement." *Id.* at 632, 634. Similarly, in *United Therapeutics*, the defendant "carved out of its proposed label all references and any instruction to use Sterile Diluent for Flolan as a diluent for intravenous administration of" the labeled drug. *United Therapeutics*, 2014 WL 4259153 at *9. Despite this carve out, the plaintiff argued that the warnings and precautions in the label were "'so unusual' and 'so severe' that they amount[ed] to an implicit instruction to physicians to dilute [Defendant's] generic product with Sterile Diluent for Flolan." *Id.* at *13. Specifically, the plaintiff argued that the warnings in the

label would cause physicians to do subsequent research that would lead them to various pieces of scholarly literature recommending the use of Sterile Diluent for Flolan, which they would inevitably elect to prescribe with the defendant's generic product. *See id.* at *17. In concluding that the label did not encourage infringement of the method patent, the Court described the plaintiff's theory as proposing "a scholarly scavenger hunt—which *may* be incited by a reference in [Defendant's] proposed label, which *may* be undertaken by some physicians, and *may* ultimately result in a discovery which leads some physicians to prescribe SDF as diluent for Defendant's generic product . . . ." *Id.* at *19.

Unlike in *Vita-Mix* and *United Therapeutics*, Defendants here made no attempt to carve out or alter the Multaq® label to discourage the use of dronedarone in patients with at least one cardiovascular risk factor. Instead, Defendants merely copied the label for Multaq®, which showcases the infringing method of treatment. Moreover, unlike in *Takeda* and *United Therapeutics*, Sanofi's theory of inducement does not require a prescribing physician to look outside the label or go on the type of "scholarly scavenger hunt" those courts eschewed. Instead, all that Sanofi's theory of inducement essentially requires is that a prescribing physician actually read Defendants' labels. Neither parties' expert suggested that a prescribing physician would not read the drug's label before prescribing it to patients. Furthermore, *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042 (Fed. Cir. 2010) demonstrates that inducement need not be premised on explicit instructions to perform the infringing method, where the proposed label "would inevitably lead some consumers to practice the claimed invention." 633 F.3d at 1060. Like in *AstraZeneca*, Defendants also have "presented no evidence that [they] attempted to draft a non-infringing label." *Id.* at 1058. In any event, I think the factual circumstances here, where the

relevant inducing information is plainly contained in Defendants' proposed labels, provide a far more straightforward example of inducement than the label at issue in *AstraZeneca*.

Accordingly, I conclude that Sanofi has proven by a preponderance of the evidence that Defendants' proposed labels induce infringement of claims 1–3, 6, 8–9, 11–13, and 16 of the '167 patent.

b. Inducement of Claims 4, 5, and 10

Defendants also separately dispute whether their labels induce infringement of claims 4, 5, and 10 of the '167 patent. Claim 4 is directed to "[t]he method according to claim 1, wherein said patient further receives a diuretic-based treatment." (JTX 3, '167 patent, claim 4). Claim 5 is directed to "[t]he method according to claim 4, wherein said diuretic is a non-potassium-sparing diuretic." (*Id.*, claim 5).

In the section of Defendants' labels describing the ATHENA trial, the labels explain that ATHENA patients were treated with dronedarone "in addition to conventional therapy for cardiovascular diseases that included," among other treatments, diuretics, which were being taken by 54% of the ATHENA patients. (JTX 257 at 508). The labels further explain, "The reduction in cardiovascular hospitalization or death from any cause was generally consistent in all subgroups based on baseline characteristics or medications," including diuretics. (*Id.* at 510). The labels also warn that "hypokalemia or hypomagnesemia may occur with concomitant administration of potassium-depleting diuretics." (*Id.* at 496).

The extent of Defendants' argument as to these claims is that almost half of the ATHENA patient population did not take a diuretic, and that Dr. Zusman testified that there is nothing in the labels that explicitly directs doctors to administer dronedarone to patients taking diuretics. (D.I. 305 at pp. 5–6; Tr. at 193:16–19). Dr. Kim, on the other hand, testified that

diuretics cause the production of urine, in order to remove salt from the body, and are commonly used to treat conditions such as hypertension and heart failure. (Tr. at 118:14–21). Dr. Kim testified that Defendants' labels make clear that dronedarone's dramatic reduction in cardiovascular hospitalization was maintained even when taken simultaneously with other types of cardiovascular treatments, including diuretics, and thereby "clearly [provide] an encouragement of the use of dronedarone in patients treated with diuretics and in accordance with claim 4." (Tr. 119:3–22). Lastly, Dr. Kim testified that the labels' safety instructions for taking dronedarone with potassium-depleting-diuretics, which are the same thing as non-potassium-sparing diuretics, demonstrates intent to ensure the two can be taken together by providing a warning to avoid negative effects. (Tr. 120:5–121:4). I credit Dr. Kim's testimony that diuretics are commonly used to treat various common cardiovascular conditions. Likewise, I think the fact that over half of the ATHENA population was taking diuretics, and that the diuretics did not decrease positive outcomes from dronedarone, would encourage at least some physicians to administer dronedarone concomitantly with diuretics. While I think a finding of inducement is less compelling here than with the issue raised as to the risk factors, I find that Sanofi has proven by a preponderance of the evidence that Defendants knew that their proposed labels "would inevitably lead some [physicians]" to administer dronedarone in conjunction with a diuretic-based treatment, according to claim 4. *AstraZeneca*, 633 F.3d at 1060. However, I find that the labels' warning about the serious side effects that can result from concomitant administration of potassium-depleting diuretics cannot reasonably be viewed as encouraging the use of dronedarone in conjunction with non-potassium sparing diuretics, according to claim 5. *See, e.g.*, *United Therapeutics*, 2014 WL 4259153, at *18, *21 (holding that "the warnings in [Defendant's] proposed label are not instructions encouraging physicians" and noting "that there

is a rather significant difference between a warning and an instruction"). Accordingly, I conclude that Defendants' proposed labels induce infringement of claim 4 of the '167 patent, but do not induce infringement of claim 5.

Lastly, Claim 10 is directed to "[t]he method of claim 1, wherein the administration of said effective amount is maintained for at least 12 months." (JTX 3, '167 patent, claim 10). Defendants argue that "[t]here is [] nothing in the labels that instructs doctors or patients to remain on dronedarone for at least twelve months." (D.I. 305 at 6). Both parties' experts, Dr. Kim and Dr. Zusman, testified that atrial fibrillation is a chronic disorder and that when they prescribe dronedarone to an AF patient they intend for the patient to take it indefinitely. (Tr. 121:14–22 (Dr. Kim); Tr. 287:18–288:6 (Dr. Zusman)). Dr. Kim pointed out that Defendants' labels specify that the ATHENA patients were treated for up to 30 months, with a median treatment time of 22 months. (Tr. 121:16–22; DTX 257 at 508). Dr. Kim further noted that Defendants' labels give safety and monitoring information, including suggesting that patients undergo cardiac rhythm assessment every three months and be checked for adverse effects during the first six months, which suggest that the drug is intended for long-term use. (Tr. 121:23–122:16; JTX 257 at 495–97).

I find that the description of the long-term treatment involved in the ATHENA trial in Defendants' labels, additional clues in the labels that suggest long-term treatment, and the experts' testimony that prescribing physicians generally intend to treat patients with dronedarone for longer than 12 months, together demonstrate by a preponderance of the evidence that Defendants' labels encourage administering dronedarone for at least 12 months. Accordingly, I conclude that Defendants' labels induce infringement of claim 10 of the '167 patent.

c. Contributory Infringement (all claims)

As to contributory infringement, the issue is whether there are any substantial non-infringing uses of Defendants' generic dronedarone product falling outside the scope of the method claims of the '167 patent. Defendants argue that there are substantial non-infringing uses that fall outside of the claims of the '167 patent, because both experts and the Sanofi epidemiology study indicate that approximately 20% of patients who are prescribed Multaq® do not have a risk factor. (D.I. 305 at pp. 16–18). Sanofi contends that all of these non-infringing uses are off-label. (D.I. 299 at p. 15). Moreover, according to Sanofi, *Eli Lilly & Co. v. Actavis Elizabeth, LLC*, 435 F. App'x 917 (Fed. Cir. 2011) stands for the proposition that off-label uses cannot be considered substantial non-infringing uses as a matter of law, because it is illegal to market products for off-label uses. (*Id.*).

I conclude that there are substantial non-infringing uses for Defendants' proposed ANDA product. I do not think that *Eli Lilly* stands for the broad proposition that Sanofi asserts. In *Eli Lilly*, the court made clear that "the product sold by the defendants is labeled solely for the patented use to treat ADHD." *Eli Lilly*, 435 F. App'x at 926. The present circumstances are distinguishable, because the labels do not so clearly exclude the uses described in the E/A trials. It is beyond dispute that, unlike the original label, the new Multaq® label, which Defendants copied, does not restrict or limit the use of dronedarone only to patients with risk factors. (JTX 257 at 494; Tr. 97:7–15; Tr. 192:8–15). Both parties' experts and Sanofi's epidemiology study indicate that approximately 15% to 23% of patients who are prescribed Multaq® do not have at least one of the claimed risk factors. (DTX 110 at 26; Tr. at 102:2–8; Tr. 195:1–5). Dr. Kim testified that he prescribes Multaq® to non-risk-factor patients who "have symptomatic recurrent atrial fibrillation. . . . to help maintain sinus rhythm for relief of symptoms," but that he considers

this use to be off-label because dronedarone "is labeled only to reduce cardiovascular hospitalizations in patients with risk factors." (Tr. 99:1–100:6, 105:4–5). Dr. Zusman testified that the proposed labels are not so limiting, as they broadly state that dronedarone is indicated to reduce hospitalization for AF in patients in sinus rhythm with a history of paroxysmal or persistent AF. (Tr. 182:13–183:20).

I do not think it is necessary to conclusively resolve the parties' dispute about whether prescribing dronedarone to reduce AF recurrence is an off-label use. The proposed labels are written broadly enough so as to arguably render on-label uses in accordance with the E/A trials and certainly do not discourage such a use in any way. Numerous pieces of evidence also demonstrate that Sanofi advertises uses of Multaq® based upon the results of the E/A studies. Namely, it advertises that Multaq® reduces the risk of first AF recurrence, prolongs the time to first AF recurrence, and otherwise maintains sinus rhythm. (JTX 213 at 1–2; JTX 214 at 236–37). Indeed, Dr. Kim admitted that Sanofi advertises the fact that Multaq reduces the symptomatic burden of AF and prolongs time to first recurrence of AF as shown in the E/A studies. (Tr. 127:20–128:5). Sanofi's argument that the uses described in the E/A studies are clearly off-label is somewhat puzzling, and is not particularly credible, because if they were, Sanofi's conspicuous marketing activities would violate laws against marketing off-label uses and potentially subject it to a criminal action. *See In re Schering Plough Corp. Intron/Temodar Consumer Class Action*, 678 F.3d 235, 239–40 (3d Cir. 2012) ("Prescription drugs frequently have therapeutic uses other than their FDA-approved indications. The [Federal Food, Drug and Cosmetic Act] . . . generally prohibits manufacturers from marketing, advertising, or otherwise promoting drugs for such unapproved or 'off-label' uses." (citing 21 U.S.C. § 331(a)); 21 C.F.R. § 202.1(e)(4) ("An advertisement for a prescription drug covered by a new-drug application . . .

shall not recommend or suggest any use that is not in the labeling accepted in such approved new-drug application or supplement . . . ."). Indeed, while Multaq® was originally approved only for the use arising out of ATHENA, it appears that later FDA-approved changes to the label, supplementing the original NDA, allowed Sanofi to broaden the Multaq® label to at least arguably include the results of the E/A trials. (*Compare* DTX 323 at 157, *with* JTX 192 at 2).

Accordingly, I reject Sanofi's argument that using dronedarone to reduce the risk of first AF recurrence and to prolong the time to first AF recurrence is clearly off-label. The argument is an unconvincing, litigation-inspired explanation of its advertising activities. Thus, unlike in *Eli Lilly*, Defendants' proposed ANDA product here is not clearly labeled solely for the patented method of use. *See Eli Lilly*, 435 F. App'x at 926. Because it is undisputed that approximately 20% of dronedarone users do not have one of the claimed cardiovascular risk factors, I find that there are substantial non-infringing uses for Defendants' proposed ANDA product. Accordingly, I conclude that there is no contributory infringement of the '167 patent under § 271(c). *See Fujitsu Ltd. v. Netgear Inc.*, 620 F.3d 1321, 1326 (Fed. Cir. 2010).

B. Obviousness

1. Legal Standard

The presumption that all patents are valid is the starting point for any obviousness determination. 35 U.S.C. § 282. A patent claim is invalid as obvious under 35 U.S.C. § 103 "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." *Id.* § 103(a); *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406–07 (2007). Obviousness is a question of law that depends on the following factual inquiries: (1) the scope and content of

the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the relevant art; and (4) any objective indicia of nonobviousness. *See KSR*, 550 U.S. at 406; *see also Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1347 (Fed. Cir. 2012). A court is required to consider secondary considerations, or objective indicia of nonobviousness, before reaching an obviousness determination, as a "check against hindsight bias." *See In re Cyclobenzaprine Hydrochloride Extended–Release Capsule Patent Litig.*, 676 F.3d 1063, 1078–79 (Fed. Cir. 2012). Relevant secondary considerations include commercial success, long felt but unsolved needs, failure of others, praise, unexpected results, and copying, among others. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17–18 (1966); *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 662–63 (Fed. Cir. 2000); *Tex. Instruments, Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1178 (Fed. Cir. 1993).

To prove obviousness, a party must show that a POSA would have been motivated to combine the prior art teachings to create the claimed treatment method with a reasonable expectation of success. *See Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1291 (Fed. Cir. 2013). The improvement over prior art must be "more than the predictable use of prior art elements according to their established functions." *KSR*, 550 U.S. at 417. Evidence of obviousness, however, especially when that evidence is proffered in support of an "obvious-to-try" theory, is insufficient unless it indicates that the possible options skilled artisans would have encountered were "finite," "small," or "easily traversed," and "that skilled artisans would have had a reason to select the route that produced the claimed invention." *In re Cyclobenzaprine Hydrochloride*, 676 F.3d at 1072. Obviousness must be proven by clear and convincing evidence. *Id.* at 1078.

2. Findings of Fact

1. The '167 patent is entitled to a priority date of February 11, 2009 based on provisional application No. 61/151,611.

2. A POSA in 2008 with respect to the '167 patent was a clinician with a medical degree who was board certified either in cardiology or electrophysiology and had at least two years of clinical experience after fellowship, and because of such fellowship, would have had some knowledge of the design, implementation, and analysis of clinical studies.

3. The ATHENA clinical trial was the first large AF trial that did not use an endpoint directly related to AF, such as prevention of recurrent AF or time to first AF recurrence. Accordingly, no AAD, including dronedarone, had previously demonstrated an ability to reduce the risk of cardiovascular hospitalization or hospitalization for AF.

4. Hohnloser 2008, written in January 2008, is prior art to the '167 patent. Hohnloser 2008 is principally written by investigators involved in the ATHENA clinical trial and outlines the rationale and design of ATHENA. A POSA in 2008 would view the statement in Hohnloser 2008—that "it is expected that treatment with [dronedarone] will result in a significant reduction in the need of rehospitalizations for cardiovascular reasons"—as the hypothesis to be tested by the ATHENA trial.

5. A post-hoc analysis in the context of a clinical trial is a retrospective analysis of clinical data that seeks to answer a question that was not a pre-specified endpoint in the original clinical trial. A POSA in 2008 would know that post-hoc analyses have inherent limitations in terms of reliability and would therefore critically evaluate conclusions arising out of a post-hoc analysis in light of the known risks and benefits of a particular method of treatment.

6. The ANDROMEDA trial, which involved giving dronedarone to patients with symptomatic heart failure and severe left ventricular systolic dysfunction, was terminated prematurely after dronedarone appeared to cause an increase in mortality due to worsening heart failure. Even though AF was not an entry criteria in the ANDROMEDA trial, AF patients commonly have underlying heart disease and 40% of the ANDROMEDA patients actually had AF. For these reasons, the ANDROMEDA trial would temper a POSA's expectations with regard to dronedarone's ability to be effective in reducing cardiovascular and AF hospitalizations. The ANDROMEDA trial also led to skepticism in the art as to dronedarone's future commercial viability.

7. Dronedarone has both rate control and rhythm control properties. Other AADs, including amiodarone and solatol, also contained such properties. As of 2008, a POSA would understand that the long term benefits of treating patients with AADs to maintain sinus rhythm were not clearly proven.

8. No prior clinical studies had demonstrated a causal link between a drug's ability to reduce AF recurrences and its ability to reduce the risk of cardiovascular hospitalization. The post-hoc analysis of the EURIDIS and ADONIS studies demonstrated results inconsistent with this assumption.

9. In 2008, POSAs considered dronedarone's efficacy in reducing AF recurrences to be modest compared to other AADs and outweighed by its potential for adverse effects.

10. In 2008, there was a need in the market for AADs with a favorable side effect profile. Other brand-name drug companies failed in efforts to develop such a drug. Multaq has a market share of 11% and a dollar market share of 50% in the field of AADs.

3. Conclusions of Law

Defendants argue that the asserted claims of the '167 patent are invalid for obviousness. Specifically, Defendants argue that a POSA in 2008 would have been motivated to treat AF patients with dronedarone, having the reasonable expectation that it would reduce the risk of cardiovascular hospitalization and hospitalization for AF. Defendants' obviousness case focuses heavily on two particular pieces of prior art, a January 2008 article in the *Journal of Cardiovascular Electrophysiology* about the rationale and design of the ATHENA clinical trial ("Hohnloser 2008") and the actual clinical trial protocol for ATHENA ("ClinicalTrials.gov"). (JTX 35; DTX 15). Defendants' theory of obviousness combines either of these two references with an October 2006 Public Assessment Report from the European Medicines Agency ("2006 EMEA Report"), which discloses taking dronedarone twice a day with a morning and evening meal. (Tr. 273:1–8; JTX 32). Sanofi does not contest that Hohnloser 2008 and Clinicaltrials.gov both disclose all but two of the elements of the asserted independent claims (1 and 8) of the '167 patent. (Tr. 672:22–676:21; JTX 35 at 69–72; DTX 15 at 1–3). Sanofi argues that Hohnloser 2008 and ClinicalTrials.gov do not disclose (1) the results of ATHENA that actually demonstrate the clinical benefit of reducing cardiovascular hospitalization, and (2) administering dronedarone twice a day with a morning and an evening meal. (D.I. 306 at pp. 4–24; Tr. 673:17–675:12). However, Sanofi does not dispute that the 2006 EMEA Report discloses that dronedarone should be administered twice a day with a morning and an evening meal. (JTX 32 at 5 ("Multaq should be taken as one tablet with or shortly after the morning meal and one tablet with or shortly after the evening meal."); Tr. 677:21–678:1). Sanofi thus does not

argue in its brief that administering dronedarone twice a day with a morning and evening meal would not be obvious to a POSA.

Accordingly, the parties' obviousness dispute revolves around one central issue, whether a POSA would have expected dronedarone to reduce the risk of cardiovascular hospitalization and hospitalization due to AF in the ATHENA patient population. Defendants point to one particular statement in Hohnloser 2008 as purportedly dispositive evidence that a POSA in 2008 would have had a reasonable expectation that dronedarone would reduce the risk of cardiovascular hospitalization:

> Since it was shown that dronedarone is not only capable of maintaining [sinus rhythm] in many patients, but also of controlling heart rate in case of AF relapses, it is expected that treatment with this compound will result in a significant reduction in the need of rehospitalizations for cardiovascular reasons.

(JTX 35 at 72). Defendants assert that Hohnloser 2008 thus "summarized the rationale and design of the ATHENA clinical trial and predicted the results of the trial . . . ." (D.I. 300 at p. 17; *see also id.* at p. 7). Defendants therefore argue that a POSA in 2008, and Sanofi itself, "expected dronedarone to reduce cardiovascular (including [AF]) hospitalizations" in ATHENA patients and that "ATHENA was designed to merely confirm that expectation." (*Id.* at pp. 16–17). Defendants further contend that the expectations described in Hohnloser 2008 had been previously stated in a number of publications, all of which discussed the results of a post-hoc analysis of data from the earlier E/A trials. (*Id.* at pp. 18–19). Thus, according to Defendants, a POSA in 2008 "would have a high expectation of success in reducing cardiovascular hospitalizations, including hospitalization for [AF], with dronedarone." (*Id.* at p. 19).

Sanofi argues that the statement Defendants rely on from Hohnloser 2008, in the context of a document explaining the rationale and design of a clinical trial, would be understood by a POSA to be merely a hypothesis to be tested by the clinical trial itself. (D.I. 306 at pp. 4–5).

Sanofi further contends that even if that statement truly expressed a concrete expectation of success, it was only a single item of information that a POSA would have considered in assessing whether it was reasonably likely that dronedarone would reduce the risk of cardiovascular hospitalization in the ATHENA population. (*Id.* at p. 5). More specifically, Sanofi argues that a POSA would critically evaluate the Hohnloser 2008 statement in light of the fact that no other AAD to date, including drugs with properties similar to dronedarone, had demonstrated an ability to reduce cardiovascular hospitalization. (*Id.* at pp. 4–8). Sanofi points out that the efficacy of dronedarone was considered modest before ATHENA, and its benefits were viewed by most in the art as being outweighed by its adverse effects, especially in light of the failed ANDROMEDA trial. (*Id.* at pp. 11–15). Sanofi further contends that a POSA would know that post-hoc analyses are inherently unreliable, that the post-hoc data from E/A was inconsistent, and that a POSA would recognize that the patient population in ATHENA was considerably different than the patient population in the E/A studies. (*Id.* at pp. 19–21).

Defendants' expert, Dr. Zusman, testified that statements in Hohnloser 2008, such as "'Dronedarone reduced the risk of rehospitalization by approximately 20 percent in the two pivotal efficacy trials,'" and, "'Thus, the overall decrease of risk for the primary endpoint in ATHENA is assumed to be 15 percent at one year,'" would be interpreted by a POSA as concrete factual statements about dronedarone's efficacy, without reservation. (Tr. 229:6–231:22; JTX 35 at 71–72). Moreover, he testified that a POSA would interpret the "it is expected" statement in Hohnloser 2008 to be a clear indication that dronedarone would likely reduce cardiovascular hospitalization, based upon dronedarone's ability both to reduce AF recurrence, as shown in the E/A trials, and to control heart rate:

> I think a person of ordinary skill in the art would have read this statement and thought, well, if they're going to do this trial, the outcome is pretty much anticipated

> and obvious. They certainly expect that treatment with Dronedarone would result in the reduction in the need for rehospitalization for cardiovascular reasons. It's pretty well outlined in this statement.

(Tr. 232:17–233:19). Dr. Zusman further testified that the Clincialtrials.gov reference's title and brief summary, listing the ATHENA trial's primary efficacy parameter to be the combined endpoint of cardiovascular hospitalization and death, suggest to a POSA that dronedarone will reduce the risk of cardiovascular hospitalization. (Tr. 233:20–235:17; DTX 15 at 1). Dr. Zusman also points out that the initial Written Subject Information ("WSI") provided to ATHENA trial patients stated the expectation that dronedarone would reduce admissions to the hospital and prolong the time in normal heart rhythm. (Tr. 236:1–237:24; DTX 24).

Dr. Zusman also testified that the failed ANDROMEDA trial involving dronedarone, which led to increased mortality, would not discourage a POSA from having a reasonable expectation that dronedarone would reduce the risk of cardiovascular hospitalization. (Tr. 238:15–21). Specifically, he asserted that because ANDROMEDA "was a study of patients with congestive heart failure in which a minority of the patients had atrial fibrillation" while every patient in ATHENA and E/A "had to have a history or be currently in atrial fibrillation," "the characteristics of the patient cohorts were so different as to make them non-relevant to one another." (Tr. 238:22–239:13). Dr. Zusman's ultimate conclusion was that:

> Based upon the clinical properties of dronedarone, demonstrated to a person of ordinary skill in the art in the EURIDIS and ADONIS trials, the ability of the drug to delay the occurrence of atrial fibrillation and its ability to reduce the heart rate of patients when they went into atrial fibrillation, not only as a person of ordinary skill in the art but others certainly concluded that dronedarone would, in fact, reduce the incidents of cardiovascular hospitalizations and/or death in the atrial fibrillation patient population with paroxysmal or persistent atrial fibrillation.

(Tr. 275:1–13).

Sanofi's expert on validity, Dr. James Reiffel, testified that a POSA would view the "it is expected statement" in Hohnloser 2008 upon which Defendants rely as a statement of the hypothesis that is going to be tested in the ATHENA trial. (Tr. 615:22–616:17). He also testified that having the ability both to maintain sinus rhythm and to control heart rate is not a property that is unique to dronedarone, but instead is shared by both amiodarone and solatol, which were involved in the "rate versus rhythm" trials.[5] (Tr. 616:18–617:5). Dr. Reiffel further opined that a POSA would not rely on the E/A post-hoc analysis to draw an expectation about dronedarone's effect on the ATHENA population, because the ATHENA population was an older, higher-risk population than that studied in the E/A trials. (Tr. 618:19–620:2). This is significant, he explained, because clinical trials involving AADs have "repeatedly [shown] that the same drug in different populations can give markedly different results." (Tr. 619:2–14). In fact, Dr. Reiffel explained that because the ATHENA population included patients with structural heart disease and previous heart failure, it was in some ways more similar to the population from the failed ANDROMEDA trial than the E/A trials. (Tr. 625:20–627:4). Dr. Reiffel further emphasized that even after ATHENA, dronedarone is the only AAD that is proven to reduce cardiovascular hospitalization and hospitalization for AF. (Tr. 648:6–9).

Dr. Reiffel also pointed out that numerous documents relied upon by Defendants, and the data underlying the hypothesis in Hohnloser 2008 and the endpoint discussed in

[5] The rate versus rhythm trials "were a series of trials commonly known . . . in the medical literature," which included the PIAF study, the RACE study, the AFFIRM study, the STAF study, the HOT CAFÉ study, and AF-CHF study. (Tr 552:20–553:20; PTX 242, PTX 334; PTX 340; PTX 342; PTX 343). The AFFIRM study was the largest of the rate versus rhythm trials, was done largely in North America, and was published in a 2002 article in the *New England Journal of Medicine*. (Tr. 553:5–8; PTX 242). The trials generally involved high-risk AF patients who were administered common AADs available at the time (amiodarone, solatol, and IC drugs), and several different endpoints, but largely showed no improvement in cardiovascular outcomes from using rhythm control drugs compared to rate control drugs. (Tr. 554:10–557:18). For instance, in the AFFIRM trial, the results showed no difference in mortality (the primary endpoint) but actually demonstrated increased hospitalization in the group taking rhythm control drugs. (Tr. 555:23–556:1).

Clinicaltrials.gov, were based on a post-hoc analysis of data from the E/A trials. (Tr. 612:8–613:12). Dr. Zusman's testimony makes little mention of the post-hoc nature of much of this data. A key issue for the Court to consider is thus how a POSA would view a post-hoc analysis of the clinical data arising out of the E/A trials.

A post-hoc analysis is essentially a retrospective analysis of clinical data that looks for trends and seeks to answer questions that were not the pre-specified questions, or endpoints, that the original clinical trials sought to evaluate. (Tr. 499:18–23). Dr. Ronald Thisted, a biostatistician who teaches medical students courses on biostatistics and interpreting clinical data, testified that post-hoc analyses "have a number of limitations" making them "unreliable for predicting the results of a future study or clinical practice." (Tr. 500:14–18). While Dr. Thisted suggested that post-hoc analyses are useful tools for mining clinical trial data and generating hypotheses, he testified that they are limited in value in that there is "an increased likelihood that the nominally significant results are, in fact, due to chance." (Tr. 501:18–503:10). He also testified that post-hoc analyses are often selectively reported. (Tr. 507:5–18). Dr. Thisted supported his testimony with citations to various articles and textbooks discussing the weaknesses of post-hoc analyses. (*See, e.g.*, PTX 456 at 181, Rothwell, *Subgroup Analysis in Randomised Controlled Trials: Importance, Indications, and Interpretation* (2006) ("Post hoc observations are not automatically invalid (many medical discoveries have been fortuitous), but they should be regarded as unreliable unless they can be replicated.")).

Dr. Reiffel testified that the E/A post-hoc analyses would not have led a POSA to conclude that dronedarone would likely reduce cardiovascular hospitalization or hospitalization for AF in the ATHENA population. (Tr. 605:16–606:1). Dr. Reiffel pointed out that, when looking at the two trials separately rather than their combined results, the post-hoc analysis

showed "discordant results" in that the European version of the trial (EURIDIS) showed a statistically significant reduction in cardiovascular hospitalizations, while the American version (ADONIS) did not. (Tr. 606:3–22; Tr. 609:16–610:16). However, in the original analysis of the E/A trials, dronedarone's ability to reduce time to first recurrence of AF, the primary endpoint in the E/A trials, was significantly greater in the ADONIS trial than in the EURIDIS trial. (Tr. 609:16–610:16). The finding from the post-hoc analysis of EURIDIS of greater efficacy for one metric (cardiovascular hospitalization) was inconsistent with the finding from the analysis of ADONIS of greater efficacy with regard to the E/A trial's primary endpoint (reduction in time to first recurrence of AF). Accordingly, Dr. Reiffel explained that "if, in fact, the suppression of [AF] and the antiarrhythmic benefit of the drug, rather than chance, led to the results, you would expect the better the suppression of [AF], the greater the likelihood of reducing hospitalization and mortality." (Tr. 609:23–610:5). Dr. Reiffel further asserted that the results of the post-hoc analysis were likely the result of chance, because while the post-hoc analysis showed that all-cause hospitalizations and all-cause deaths occurred with 22% of patients treated with dronedarone versus 30.9% in the placebo group, there was only a 3.1% difference (16.1% vs. 19.2%) between the rate of cardiovascular hospitalizations or death in the dronedarone group versus the placebo group. (Tr. at 611:2–17). Dr. Reiffel explained that it did not make sense that dronedarone, being an AAD meant only to treat heart conditions, had a much greater impact on all-cause hospitalizations and all-cause death than on cardiovascular hospitalizations. (Tr. 611:18–612:7). Thus, according to Dr. Reiffel, a POSA would view the reduction in all-cause hospitalizations or death shown in the post-hoc analysis of the E/A results as likely the result of chance. (*Id.* ("I can't provide the mechanism by which the drug would reduce non-CV hospitalizations, so I have to assume this is one of the results by chance . . . .")).

In light of the overall evidence, I conclude that a POSA in 2008 would not have had a reasonable expectation that dronedarone would reduce the risk of cardiovascular hospitalization and hospitalization for AF in patients with paroxysmal or persistent AF and the associated risk factors of the ATHENA patient population. I find that the statement from Hohnloser 2008 that Defendants heavily rely on, that "it is expected that treatment with this compound will result in a significant reduction in the need of rehospitalizations for cardiovascular reasons," would not be read in isolation and taken at face value by a POSA, without appropriate context. (JTX 35 at 72). With regard to the article itself, Hohnloser 2008 is a brief article describing the rationale and design of the ATHENA clinical trial before any results were reported, and is principally written by the investigators involved in the trial. (*Id.* at 69–72). Defendants key in on the language "it is expected that," but reading Hohnloser 2008 in its entirety shows that this statement is tempered to reflect the fact that this was an important clinical trial for the future of dronedarone. The article describes the ATHENA clinical trial as being "of paramount importance for the future of dronedarone." (JTX 35 at 70). Moreover, the article explains that the ANDROMEDA trial, although "not an AF study," produced "increased mortality in patients with a recent history of decompensated heart failure." (*Id.* at 72). Hohnloser 2008 thus explained that the findings of ANDROMEDA "reemphasize[d] the need for a large dronedarone outcomes study in a typical population of elderly AF patients." (*Id.*). In other words, the ANDROMEDA findings reinforced the need to perform the ATHENA trial. The article also indicated that in targeting the combined endpoints of all-cause mortality and cardiovascular hospitalization, "ATHENA [was] the first large AF trial which does not use any 'conventional' endpoint directly related to AF such as prevention of recurrent AF, time to first AF recurrence, AF burden or others." (*Id.*). The central conclusion of the document was not the likely result of

the trial, but simply that "ATHENA will be the largest efficacy and safety trial of dronedarone, a multichannel blocker compound with properties from class I, II, III, and IV antiarrhythmic drugs developed to treat patients with AF." (*Id.* at 69). Reading the document in this proper context, I credit Dr. Reiffel's testimony that the "it is expected" statement from Hohnloser 2008 represents a hypothesis that requires future testing, rather than a concrete expectation of success. (Tr. 616:9–17).

Other documents relied upon by Defendants (*see* D.I. 300 at pp. 9–11, 18–19) simply report on the findings of the same post-hoc analysis of the E/A data and expressly state that these findings are based on post-hoc analysis. Moreover, the post-hoc analysis measured the recurrence of all-cause hospitalization or death, rather than cardiovascular hospitalization specifically. For instance, a 2007 article in the *New England Journal of Medicine*, which describes the EURIDIS and ADONIS trials ("Singh 2007"), merely states, "in a post hoc analysis, dronedarone significantly reduced the rate of hospitalization or death." (JTX 170 at 995). Another reference, an abstract published in the *Circulation Journal of the American Heart Association* reporting on a presentation from a meeting ("Hohnloser 2005"), simply states, "We conducted a post-hoc analysis [of the EURIDIS/ADONIS results] to evaluate the potential clinical benefit of [dronedarone] at reducing hospitalizations or death," and reported that dronedarone "reduced the combined endpoint of hospitalization or death in [patients] with AF." (JTX 221 at 1637). Hohnloser 2005 also noted that this result was a significant departure from "the perceived less optimal safety of existing antiarrhythmic drugs." (*Id.*). The remainder of the documents upon which Defendants rely simply report on the same results from the same post-hoc analysis. (*See, e.g.*, JTX 172 at 1–2 ("Stein 2005"); JTX 220 at 65 ("Jancin 2006"); JTX 28 at 220 (internal Sanofi document); JTX 55 at 1 (Sanofi's WSI for ATHENA trial); JTX 47 at 16

(Athena Clinical Trial Protocol); JTX 48 at 22 (ATHENA clinical study report); JTX 34 at 31:1–3 (FDA Transcript); JTX 173 at 3–4 (Multaq Briefing Document to the FDA advisory committee meeting)).

Dr. Zusman testified that a POSA would look at Hohnloser 2008 and Clinicaltrials.gov, two references essentially outlining the structure and goals of the ATHENA clinical trial, and conclude that it was obvious that the trials would successfully hit their primary endpoint. In essence, his testimony is that a POSA would take statements of "expectation" in these two documents at face value, without further critical evaluation, and conclude that dronedarone would reduce cardiovascular hospitalization in the chosen patient population. Dr. Zusman testified that dronedarone has properties—the ability to both maintain sinus rhythm and control heart rate—that would lead a POSA to conclude it would likely reduce cardiovascular hospitalization. (Tr. 275:1–13). But Dr. Zusman admitted that as of 2008 having both of these properties was not unique to dronedarone; both amiodarone and solatol had been proven effective at maintaining sinus rhythm in patients with AF and reducing ventricular rate during AF relapses. (Tr. 292:12–293:21). Moreover, he admitted that no studies had shown that amiodarone or solatol could reduce cardiovascular hospitalization, and that no studies had demonstrated a causal link between the ability to reduce AF recurrences and reducing cardiovascular hospitalization more generally. (Tr. 293:6–12, 294:1–5, 289:8–291:8).

I credit Dr. Reiffel's testimony that a POSA in 2008 would have critically evaluated statements of "expectation" in documents outlining the rationale and design of a clinical trial, especially in light of the post-hoc nature of the data and the overall history of unexpected results in trials involving dronedarone and other antiarrhythmic drugs, discussed *infra*. I think that a POSA would give some weight to a post-hoc analysis but would not blindly accept one at face

value and conclude that a specific treatment regimen would be successful. Moreover, I think that the extent that a POSA would rely on post-hoc analyses may differ based on the known risks associated with particular forms of treatment and/or conditions being treated. In the specific context of antiarrhythmic drugs and dronedarone specifically, there are three principal reasons why I credit Dr. Reiffel's testimony that a post-hoc analysis of the E/A trial data would alone not give a POSA a reasonable expectation that administration of dronedarone would reduce cardiovascular hospitalizations and hospitalizations due to AF.

First, many of the documents relied upon by Defendants in attempting to establish obviousness support the suggestion that post-hoc analyses have inherent limitations, because their conclusions emphasize that they are based only on results from post-hoc analyses. For instance, the Jancin 2006 article described the post-hoc analysis results as demonstrating a "potential major clinical benefit," and reported that "Dr. Hohnloser stressed that 'potential' needs to be emphasized because this was a post-hoc analysis . . . ." (JTX 220 at 65; *see also* JTX 172 at 1 ("Stein 2005") (explaining that reduction in cardiovascular hospitalization was a "potential clinical benefit [that] is currently being assessed in a large outcome study . . . ATHENA . . . .")). Moreover, the WSI given to potential participants in the ATHENA trial explained that the "long term benefit" of treating patients with AADs to maintain sinus rhythm "is not clearly proven as of today and also the tolerability of some of these drugs is not very satisfactory." (JTX 55 at 1). The WSI also described the benefits shown by the post-hoc analysis of E/A data to prospective patients in less than certain terms. "It also appeared in these studies that patients treated with dronedarone were less frequently admitted to a hospital." (*Id.*). The 2006 EMEA report also downplayed the import of the E/A post-hoc analysis. "A reduction in time to death and hospitalization was noted but this reflects an ancillary analysis and needs further

confirmation . . . ." (JTX 32 at 19). Lastly, in a March 18, 2009 hearing before the FDA, on which Defendants rely, Dr. Jerry Naccarelli described the post-hoc analysis of the E/A data as showing "a favorable trend that just missed statistical significance" and "giving a signal and *generating a hypothesis* that this drug, in a prospective large randomized trial, might meet this end point . . . ." (JTX 34 at 30:8–15 (emphasis added)). Accordingly, I find that these various statements support Dr. Reiffel's testimony that a POSA would not view the E/A post-hoc analyses as describing any sort of scientifically reasonable likelihood that dronedarone would successfully reduce the risk of cardiovascular hospitalization in patients with persistent or paroxysmal AF and the associated risk factors.

Second, I think that the clinical history of dronedarone itself, in particular the fact that its use resulted in increased mortality during the ANDROMEDA trial, would counsel a POSA against giving too much weight to the results of a post-hoc analysis without further experimentation. The ANDROMEDA trial, which involved patients recently hospitalized with symptomatic heart failure and severe left ventricular systolic dysfunction, was terminated prematurely after dronedarone appeared to cause an increase in mortality due to worsening heart failure. (JTX 257 at 512; Tr. 599:14–23). The parties largely do not dispute that the ANDROMEDA population was a sicker population than the ATHENA population or that ANDROMEDA was not an AF trial. (Tr. 361:10–18; Tr. 146:1–147:2). But it is also true that ATHENA involved a sicker population than EURIDIS and ADONIS. ATHENA involved older patients, who had to have at least one of various cardiovascular risk factors, and even included some patients with heart failure, while EURIDIS and ADONIS did not. (Tr. 144:19–145:20; 625:20–628:18). EURIDIS and ADONIS simply involved a population with paroxysmal and persistent AF. (Tr. 625:20–626:5; JTX 257 at 511–12). In any event, because AF patients often

have underlying heart disease and some of the ANDROMEDA patients actually had AF, I do not think a POSA would simply disregard ANDROMEDA just because AF was not a required patient characteristic. (Tr. 625:20–627:4; PTX 379 at 372). In fact, an August 2006 letter from the FDA rejected Sanofi's NDA for dronedarone based on the E/A results, explaining that the risks associated with dronedarone, especially those shown in ANDROMEDA, did not justify approval based on its modest benefits compared to its potentially deadly side effects:

> There is no doubt that dronedarone HCl 400 mg twice daily increases the time to recurrent AF modestly and slows the ventricular response by about 10 beats per minute. The data, however, do not indicate a favorable risk-benefit relationship for either rate control or prevention of AF recurrence. As all antiarrhythmic agents raise concerns of pro-arrhythmic or otherwise adverse cardiovascular effects, their use to control symptoms needs to be supported by an assessment of their potential for serious harm. The ANDROMEDA study was intended to provide reassurance about this potential by showing a low upper bound for dronedarone's possible adverse effect on mortality in a high-risk population. ANDROMEDA did not provide such reassurance, instead showing increased mortality, causing the Data Monitoring Committee for the trial to urge its interruption. *Apart from ANDROMEDA's failure to provide general reassurance, as patients with AF commonly have underlying heart disease, the ANDROMEDA result seems particularly applicable to that population.*

(PTX 379 at 372 (emphasis added)). The 2006 EMEA Report similarly reported that the E/A post-hoc analysis was "an ancillary analysis [that] needs further confirmation, in particular in the context of the negative effects seen in [] ANDROMEDA." (JTX 32 at 19). Accordingly, the FDA's non-approval letter and the EMEA report provide additional support for Dr. Reiffel's opinion that a POSA would critically assess the hypothesis from the E/A post-hoc analysis, especially in light of ANDROMEDA.

Third, while less relevant than ANDROMEDA, I find that the historic uncertainty in the field regarding the efficacy of AAD treatments generally and the lack of consistent clinical trial results are factors that would cause a POSA to take a more exacting look than usual at a post-hoc

analysis. Dr. Reiffel explained that uncertainty in treating cardiac arrhythmias traces back originally to the CAST trials in the late 1980s and early 1990s. (Tr. 540:6–541:8). These trials tested the hypothesis that giving AADs to suppress extra ventricular beats would decrease mortality, but the trials were shut down prematurely due to an increase in mortality of nearly three times more than the placebo. (Tr. 541:9–542:17). Dr. Reiffel explained that the CAST trials "had a negative impact on antiarrhythmic drug usage" and that the FDA began requiring an affirmative showing that any new antiarrhythmic drug formulation did not increase mortality. (Tr. 547:1–14; *see also* PTX 404 at 1 ("[A]fter CAST, the FDA changed its advice regarding antiarrhythmic drugs and required evidence showing minimally, that a new antiarrhythmic agent did not cause death in patients."). Dr. Reiffel also explained that the rate versus rhythm trials, which involved amiadarone and solatol and occurred throughout the early 2000s, showed results indicating that a rhythm control approach to treating AF offered no improvement over rate control approaches, and even that rhythm control drugs showed increased hospitalization relative to rate control drugs, at least in the AFFIRM trial. (Tr. 552:20–557:18). Indeed, by 2005, Dr. Rodney Falk described, in an American Heart Association publication, how the medical community was losing faith in using antiarrhythmic agents to treat AF:

> "Common sense" may decree that being born in sinus rhythm is a reason to try and remain in it, but the era of controlled clinical trials is littered with discarded common sense arguments . . . . So it is now with atrial fibrillation. The controlled trials have consistently demonstrated no benefit of attempts to maintain sinus rhythm over rate control in any primary or secondary end point evaluated.
>
> Studies demonstrating that atrial fibrillation is associated with increased mortality do not prove that restoration of sinus rhythm will reduce mortality. Rather, they suggest that atrial fibrillation is a marker of a more severe disease . . . .

(PTX 347 at 3156).

Within this background context, Dr. Reiffel also testified that a POSA would not believe that the specific properties of dronedarone would lead it to reduce the adverse cardiovascular events, such as strokes or heart failure, that lead to hospitalizations. (Tr. at 588:7–591:1). For instance, Dr. Reiffel pointed out that data from the DAFNE trial and the E/A trials demonstrated that dronedarone only had mild efficacy in maintaining sinus rhythm. (Tr. 590:6–594:14). It follows that a POSA would not have expected that a mildly effective drug would reduce adverse cardiovascular events, when more potent antiarrhythmic drugs, such as amiodarone and solatol, had not demonstrated such a reduction in adverse cardiovascular events in previous clinical trials. (*Id.*; *see also* PTX 346 at 7 (showing that the average number of patients that needed to be treated with a particular drug to avoid one recurrence of AF was "3 for amiodarone, 4 with flecanide, 5 with dofetilide and propafenone, 8 with quinidine and solatol and 10 with dronedarone.")). Moreover, Dr. Reiffel testified that a POSA in 2008 would have known that dronedarone contained many of the same properties that were believed to have caused adverse effects in prior clinical trials involving antiarrhythmic drugs, such as the CAST trials. (Tr. 596:1–602:11).

Lastly, I think that the evidence presented on secondary considerations favors a finding of nonobviousness. For instance, I think that while there were multiple other AADs on the market, there was a need for an AAD with less adverse side effects and that could be safely taken by high-risk patients. (Tr. 636:2–638:14; PTX 416 at 926 ("It has been notoriously difficult to develop a drug with high efficacy against AF with a favorable side effect profile."); PTX 425 at 347 ("There is an urgent need for therapies with an improved balance between antiarrhythmic efficacy on one hand, and tolerability and safety on the other.")). Moreover, the fact that no other AADs, including ones with properties similar to dronedarone, have been proven to reduce

cardiovascular and AF hospitalizations, and that no such other compounds were later developed by other pharmaceutical companies, suggests that the reduction in such hospitalizations was not obvious. (Tr. 639:6–641:8). There was certainly skepticism in the art as to dronedarone's commercial viability due to safety and efficacy concerns arising after the ANDROMEDA trial. (*See, e.g.*, PTX 391 at 142 ("[E]ven though efficacy in suppressing atrial fibrillation has been demonstrated . . . the excess mortality noted in ANDROMEDA may limit [dronedarone's] commercial viability."); PTX 366 at 453 ("A higher mortality seen in ANDROMEDA . . . and reduced efficacy in maintenance of sinus rhythm compared with amiodarone reduce overall enthusiasm for dronedarone.")). Likewise, there was considerable praise for the treatment methods claimed by the '167 patent when the results of the ATHENA trial were published. (*See, e.g.*, PTX 423 at 1 ("[T]he new antiarrhythmic agent dronedarone has shown remarkable clinical results in the ATHENA trial."); PTX 424 at 421 ("Groundbreaking results indicate that dronedarone could reduce cardiovascular events in patients with atrial fibrillation."). The 4.8 million prescriptions for Multaq®, demonstrating a prescription market share of 11% and a dollar market share of 50%, demonstrate that Multaq® has been at least a moderate commercial success to this point, even if its mean sales are lower than other more established AADs. (Tr. 738:18–741:9, 834:17–835:17; PTX 263; PTX 264).[6] Dr. Reiffel's testimony that the success of Multaq® is attributable to the fact that it is the only AAD that reduces the risk of cardiovascular hospitalization strikes me as credible in light of the multitude of other more potent AADs on the market without this benefit, and provides the required nexus between commercial success and the method claims of the '167 patent. (Tr. 648:1–19).

[6] Defendants' argument as to objective indicia of nonobviousness largely points to things of marginal, if any relevance, such as the fact that Sanofi may not have done the ATHENA trial if it could have gotten FDA-approval for dronedarone after EURIDIS and ADONIS or that Sanofi markets Multaq® for some uses not covered by the '167 patent.

In sum, based on the evidence presented at trial, I think that a POSA in 2008 would have been at best cautiously optimistic that dronedarone could reduce the risk of cardiovascular hospitalization and hospitalization for AF in the ATHENA patient population. In other words, Hohnloser 2008 provided a hypothesis, based upon a post-hoc analysis, for a POSA to test through further experimentation. It is not sufficient to merely assert an "obvious-to-try theory," especially where, as here, the relevant art is littered with a history of inconsistent clinical trial results involving both dronedarone specifically and antiarrhythmic drugs generally. *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1072–73 (Fed. Cir. 2012). Indeed, in light of dronedarone's less than stellar track record in clinical trials before ATHENA and the historical uncertainty surrounding antiarrhythmic drugs, I find it much more likely that a POSA would be considerably skeptical of dronedarone's ability to actually succeed in reducing the risk of cardiovascular hospitalization and hospitalization due to AF. Moreover, I find it not credible that a POSA would simply read the outline of a future clinical trial and the results of a single post-hoc analysis, and various pieces of literature simply reporting on that same analysis' "expected benefit," and determine that dronedarone would likely provide a benefit never shown by a single other AAD, ignoring two decades of erratic results in clinical trials involving AADs. Instead, I think that while a POSA may have been motivated to try using dronedarone to reduce cardiovascular hospitalizations and hospitalizations for AF after the post-hoc analysis, a POSA in 2008 would not have had a reasonable expectation of success, given what was known about both dronedarone and other AADs. Accordingly, I conclude that Defendants have failed to prove by clear and convincing evidence that the '167 patent is invalid as obvious.[7]

[7] As with their arguments on induced infringement, Defendants do not make any separate arguments with regard to independent claim 8, which refers to a reduction in "hospitalization for atrial fibrillation," rather than just

C. Public Use

1. Legal Standard

Under 35 U.S.C. § 102(b), a patent is invalid if "the invention was . . . in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States." 35 U.S.C. § 102(b). Assessing whether the public use bar of § 102(b) applies is a two-step inquiry, and asks 1) whether the invention is "ready for patenting," and 2) whether the invention is in "public use." *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 424 F.3d 1374, 1379 (Fed. Cir. 2005). However, "evidence of experimental use . . . operates to negate application of section 102(b)." *EZ Dock v. Schafer Sys., Inc.*, 276 F.3d 1347, 1351 (Fed. Cir. 2002); *see also Pfaff v. Wells Electronics, Inc.*, 525 U.S. 55, 64 (1998) ("[A]n inventor who seeks to perfect his discovery may conduct extensive testing without losing his right to obtain a patent for his invention—even if such testing occurs in the public eye. The law has long recognized the distinction between inventions put to experimental use and products sold commercially.").

"Experimentation evidence includes tests needed to convince [the inventor] that the invention is capable of performing its intended purpose in its intended environment." *EZ Dock*, 276 F.3d at 1352 (alteration in original) (internal quotation marks omitted). "[I]n applying the [Supreme Court's] *Pfaff* two-part test in the context of a public use bar, evidence of experimental use may negate either the 'ready for patenting' or 'public use' prong." *Invitrogen*, 424 F.3d at 1379–80. For instance, demonstrating reduction to practice requires "proof that an invention will

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"cardiovascular hospitalization." Based upon the evidence, I conclude that the obviousness analysis need not differ and, if anything, the principal cause of the successful decrease in cardiovascular hospitalization shown in the ATHENA trial—a decrease in hospitalization for AF—would have been even further from a POSA's reasonable expectation than a reduction in cardiovascular hospitalization more generally. In addition, asserted claims 2–5, 6, 9, 10–13, and 16 all depend from either independent claim 1 or independent claim 8. Accordingly, because those claims inherently require either that the treatment actually reduce the risk of cardiovascular hospitalization or hospitalization for AF, I conclude that these dependent claims are also not rendered obvious.

work for its intended purpose," which evidence of continued experimentation tends to negate. *EZ Dock*, 276 F.3d at 1352. "The proper test for the public use prong of the § 102(b) statutory bar is whether the purported use: (1) was accessible to the public; or (2) was commercially exploited." *Invitrogen*, 424 F.3d at 1380. "Thus, the test for the public use prong includes the consideration of evidence relevant to experimentation, as well as, *inter alia*, the nature of the activity that occurred in public; public access to the use; confidentiality obligations imposed on members of the public who observed the use; and commercial exploitation." (*Id.*).

2. Findings of Fact

1. The ATHENA clinical trial protocol, as set forth in Hohnloser 2008 and Clinicaltrials.gov, did not disclose that dronedarone is proven to reduce the risk of cardiovascular hospitalization and hospitalization due to AF in patients with paroxysmal or persistent AF and one of the risk factors from the ATHENA patient population.

2. The inventors of the '167 patent did not know that dronedarone would reduce cardiovascular hospitalization and hospitalization for AF in the ATHENA patient population prior to April 16, 2008.

3. The investigators involved in the ATHENA clinical trial were bound by confidentiality obligations.

3. Conclusions of Law

Defendants argue that the '167 patent is invalid because the ATHENA trial was purportedly a prior public use one year before the patent's application date. (D.I. 300 at pp. 28–30). Defendants argue that "there is no dispute that dronedarone was used in the ATHENA clinical trial in a manner that meets all of the claim limitations." (*Id.* at p. 29). Defendants emphasize that none of the patients were under confidentiality restrictions and that the clinical trial protocol itself was not kept confidential. (*Id.* at pp. 29–30). Lastly, Defendants claim that the '167 patent was ready for patenting when the ATHENA trial started because "Sanofi already knew the claimed invention was operable based on its earlier studies in EURIDIS/ADONIS."

(*Id.* at p. 30). Sanofi argues that the '167 patent was not ready for patenting before the ATHENA trial results were known because the trial itself constituted critical experimentation about whether the invention could successfully treat the ATHENA patient population. (D.I. 306 at p. 29). Sanofi further contends that neither Defendants nor Dr. Zusman identified a single U.S. patient that was treated with dronedarone according to the claimed methods. (*Id.* at p. 30). Lastly, Sanofi argues that the principal investigators were subject to confidentiality agreements, which other courts have found sufficient to negate a showing of public use in the context of clinical trials. (*Id.*). The parties do not dispute that the critical date is April 16, 2008, one year before the patentee filed for the '167 patent.

I conclude that Defendants' public use argument must fail because the ATHENA clinical trial was plainly an experimental use. Indeed, a clinical trial seeking to test a particular treatment hypothesis seems to be the quintessential experimental use. *See In re Omeprazole Patent Litig.*, 490 F. Supp. 2d 381, 507 (S.D.N.Y. 2007) ("[Defendant] has not met its heavy burden of demonstrating by clear and convincing evidence that the claimed inventions had been reduced to practice during the clinical trials of the Phase III formulation and prior to the critical date. Indeed, the trials demonstrate the opposite; namely, that Plaintiffs were still in the process of determining whether the Phase III formulation could safely and effectively be used as a 'method of treatment of gastrointestinal disease.'"). The '167 patent was not "ready for patenting" merely as a result of the ATHENA protocol set forth to test a specific hypothesis. Indeed, much like in *Omeprazole*, the ATHENA trial itself demonstrated that Sanofi was still in the process of determining whether dronedarone could safely and effectively treat high-risk AF patients. *See Omeprazole*, 490 F. Supp. 2d at 507. The fact that dronedarone's clinical benefit was uncertain before the critical date is further highlighted by the fact that the FDA and EMEA essentially

required that Sanofi hold the ATHENA trial to show that dronedarone could provide a clinical benefit to patients with AF and associated risk factors in a safe and effective manner. (PTX 379 at 372; JTX 32 at 19). The ATHENA protocol certainly did not and could not provide proof that the claimed methods of treatment would work for their intended purpose, which is required to show that the invention is "ready for patenting." *See EZ Dock*, 276 F.3d at 1352. A POSA would not have had a reasonable expectation in 2008 that dronedarone would reduce cardiovascular hospitalization in the ATHENA patient population, let alone have actually known with certainty that such benefits would ensue. No other AAD had demonstrated the ability to reduce cardiovascular hospitalization before dronedarone did in ATHENA. (Tr. 293:6–294:5, 289:8–291:8 (Dr. Zusman); Tr. 648:6–9 (Dr. Reiffel)). Likewise, concerns over the increased mortality shown in the ANDROMEDA trial still existed; the ANDROMEDA result almost directly contradicts a finding of reduced risk of cardiovascular hospitalization. (PTX 379 at 372; Tr. 625:20–627:4). Accordingly, because the inventors needed to perform experimentation to see if dronedarone actually reduced cardiovascular hospitalization, Defendants have failed to prove by clear and convincing evidence that the '167 patent was ready for patenting before the critical date.

While failure to meet the ready for patenting prong alone precludes application of the public use bar, I also do not think the lack of signed confidentiality agreements from the patients renders the ATHENA trial a public use, especially in light of the other considerations that are relevant in a public use inquiry. *See, e.g.*, *Bayer Schering Pharma AG v. Barr Labs. Inc.*, 2008 WL 628592, at *38 (D.N.J. Mar. 3, 2008) ("[L]ack of confidentiality provisions for the human patients is not outcome determinative on the public nature of the use."), *aff'd*, 575 F.3d 1341 (Fed. Cir. 2009). The fact that the use was experimental negates the idea that the invention itself

was in public use. *See, e.g.*, *Invitrogen*, 424 F.3d at 1380. Moreover, simply performing a clinical trial to gain FDA approval, without more, is certainly not an act of commercial exploitation. *See In re Omeprazole*, 490 F. Supp. 2d at 509 (rejecting defendant's argument that clinical trials constituted invalidating commercial exploitations "insofar as the trials were a means of obtaining FDA approval" because such a theory "would unduly force the hand of inventors of new pharmaceutical formulations to file for patents prior to sufficiently testing the safety and efficacy of the formulation."). The investigators involved in the ATHENA trial were subject to confidentiality obligations in order to gain access to the protocol. (JTX 47 at 46; Tr. 665:1–666:4). Accordingly, the individuals to whom a method of treatment would be most significant, physicians, were held to strict confidentiality obligations. *See Bayer Schering*, 2008 WL 628592 at *40 (emphasizing that "the persons other than the inventor who participated in overseeing and observing the U.S. clinical trial, i.e., the principal investigators and study managers contracted with oversight, were all bound by confidentiality provisions."). Given all of the above circumstances, I conclude that the ATHENA clinical trial was not a public use. *See Invitrogen*, 424 F.3d at 1380.

Accordingly, I conclude that Defendants have failed to meet their burden of demonstrating by clear and convincing evidence that the '167 is invalid under § 102(b) for a public use occurring before April 16, 2008.

III. '800 PATENT CLAIM CONSTRUCTION

Before the pretrial conference, the parties exchanged motions in limine that essentially disputed the meaning of the Court's prior claim construction of "nonionic hydrophilic surfactant." (D.I. 276-1 at 350–60). Both parties conceded that the interpretation of this claim construction was the sole remaining dispute with regard to the '800 patent. At the *Markman*

stage, Defendants argued that "nonionic hydrophilic surfactant" should be construed to mean "a nonionic hydrophilic surfactant which is not a polysorbate surfactant," based upon prosecution history disclaimer. (D.I. 204 at 8–9). Although the Court adopted Defendants' proposed construction at the time, Defendants' motion in limine later argued that in doing so the Court held that the pharmaceutical composition as a whole could not include a polysorbate surfactant, even if another nonionic hydrophilic surfactant were present in an accused product to meet that claim limitation. (D.I. 276-1 at 352–54). Sanofi argued that the Court's prior construction required "a pharmaceutical composition comprising a nonionic hydrophilic surfactant which is not a polysorbate surfactant." (*Id.* at 356–58). After reviewing the *Markman* opinion and briefing, I concluded that whether the disclaimer applied to the claimed composition as a whole was not the issue presented by the parties in the *Markman* briefing, nor the issue the Court originally decided. Accordingly, I encouraged the parties to submit post-trial briefing on this claim construction issue and to give this more precise issue *de novo* consideration. In the course of thinking about this some more, I now reach a different conclusion.

A. Legal Standard

"The doctrine of prosecution disclaimer is well established in Supreme Court precedent, precluding patentees from recapturing through claim interpretation specific meanings disclaimed during prosecution." *Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1323 (Fed. Cir. 2003). "Prosecution disclaimer occurs when a patentee, either through argument or amendment, surrenders claim scope during the course of prosecution." *Heuft Systemtechnik GMBH v. Indus. Dynamics Co.*, 282 F. App'x 836, 839 (Fed. Cir. 2008). "When the application of prosecution disclaimer involves statements from prosecution of a familial patent relating to the same subject matter as the claim language at issue in the patent being construed, those statements in the

familial application are relevant in construing the claims at issue." *Ormco Corp v. Align Tech., Inc.*, 498 F.3d 1307, 1314 (Fed. Cir. 2007). Accordingly, courts "examine the patent's prosecution history, when placed in evidence, to determine whether the inventor disclaimed a particular interpretation of a claim term during the prosecution of the patent in suit or during the prosecution of an ancestor application." *Ventana Med. Sys., Inc. v. Biogenex Labs, Inc.*, 473 F.3d 1173, 1182 (Fed. Cir. 2006).

"When the purported disclaimers are directed to specific claim terms that have been omitted or materially altered in subsequent applications (rather than to the invention itself), those disclaimers do not apply." *Saunders Grp., Inc. v. Comfortrac, Inc.*, 492 F.3d 1326, 1334 (Fed. Cir. 2007). Indeed, it is well-settled that, "In general, a prosecution disclaimer will only apply to a subsequent patent if that patent contains the same claim limitation as its predecessor." *Regents of Univ. of Minn. v. AGA Med. Corp.*, 717 F.3d 929, 943 (Fed. Cir. 2013); *see also Ventana*, 473 F.3d at 1182 ("[T]he doctrine of prosecution disclaimer generally does not apply when the claim term in the descendant patent uses different language."); *Invitrogen Corp. v. Clontech Labs., Inc.*, 429 F.3d 1052, 1078 (Fed. Cir. 2005) ("[P]rosecution of one claim term in a parent application will generally not limit different claim language in a continuation application."); *ResQNet.com, Inc. v. Lansa, Inc.*, 346 F.3d 1374, 1383 (Fed. Cir. 2003) ("Although a parent patent's prosecution history may inform the claim construction of its [descendant], the [parent's] prosecution history is irrelevant to the meaning of [] limitation[s] [that] do not share the same claim language."). "The sole exception is when the disclaimer is directed to the scope of the invention as a whole, not a particular claim." *Regents*, 717 F.3d at 943 n.8.

B. Conclusions of Law

Defendants argue, "Sanofi unequivocally disclaimed all compositions containing any polysorbates" during prosecution of U.S. Patent No. 7,323,493 ("the '493 patent"), the '800 patent's parent, and failed to notify the PTO during prosecution of the '800 patent that it sought to recapture compositions containing polysorbates. (D.I. 305 at p. 19). Defendants assert that under *Heuft*, the disclaimer with respect to the parent patent applies to the child patent because the '493 patent and the '800 patent relate to the same subject matter. (*Id.* at p. 22). Defendants maintain that Sanofi was required to, but did not, expressly inform the examiner that it intended to recapture compositions containing polysorbate surfactants. (*Id.* at pp. 24–25). Thus, Defendants contend that "Sanofi is [] barred from recapturing compositions containing polysorbates by the doctrine of prosecution disclaimer . . . ." (*Id.* at p. 19).

Sanofi argues that "any disclaimer concerning polysorbate surfactants in the '493 patent cannot apply to the '800 patent because the '800 patent claims omit the limitation to which the disclaimer applied, and differ in language and scope." (D.I. 299 at p. 16). Sanofi points out that the specification of the '800 patent lists several polysorbates as exemplary surfactants and otherwise evidences no intent on the part of the patentee to exclude polysorbate surfactants from the claimed composition. (*Id.* at p. 17). Sanofi also contends that even if there were a disclaimer that carried over to the '800 patent, the prosecution history for the '800 patent demonstrates that the disclaimer was rescinded. (*Id.* at p. 23). Specifically, Sanofi points to various statements and rejections by the examiner evidencing an understanding that the applicant intended for the invention to cover polysorbates, the fact that the applicant never advanced the lack of polysorbates as a distinguishing feature, and the fact that the examiner revisited the Martin-

Algarra reference, the very prior art reference that the disclaimer in the '493 patent was meant to overcome. (*Id.* at pp. 23–25).

It is undisputed that a polysorbate surfactant is a nonionic hydrophilic surfactant. (D.I. 194 at pp. 35, 39). It is also undisputed that the '493 patent disclaimed compositions containing polysorbate surfactants after multiple rejections by the PTO under § 103 as being obvious over references disclosing polysorbate surfactants, including the Martin-Algarra reference. (D.I. 87-5 at 29–30; D.I. 87-6 at 19). After several rejections, the applicant stated its disagreement with the examiner's conclusions but ultimately amended the claims to include the extra, explicit limitation in independent claim 1, "provided that the pharmaceutical composition does not contain a polysorbate surfactant." (D.I. 87-6 at 30, 33). The applicant also distinguished these references on other grounds, including the "tablet," "oral administration," and "selected from poloxamers" limitations. (*Id.* at 30–31). The examiner then allowed the claims. (*Id.* at 41–44).

It is also not in dispute that there are some variations in claim language between the '493 patent and the '800 patent, with claim 1 of each appearing as follows:

'493 Patent Claim 1	**'800 Patent Claim 1**
1. A solid pharmaceutical composition in tablet form for oral administration comprising a benzofuran derivative with antiarrhythmic activity selected from the group consisting of dronedarone and amiodarone, or a pharmaceutically acceptable salt thereof, as an active principle, and a pharmaceutically acceptable nonionic hydrophilic surfactant selected from poloxamers, optionally in combination with one or more pharmaceutical excipients, said nonionic hydrophilic surfactant being present in a proportion of from 5% to 15% by weight of the active principle in base form, provided that the pharmaceutical composition does not contain a polysorbate surfactant.	1. A solid pharmaceutical composition for oral administration comprising *dronedarone*, or a pharmaceutically acceptable salt thereof, as an active principle, and a pharmaceutically acceptable nonionic hydrophilic surfactant optionally in combination with one or more pharmaceutical excipients wherein the nonionic hydrophilic surfactant is present in a proportion of from *1% to 50% by weight* of the active principle in base form.

The claims of the two patents, while similar, are not identical. Indeed, the '800 patent is narrower than the '493 patent in that it only covers dronedarone compositions, while the '493 patent could include amiodarone.[8] The claims of the '800 patent are also broader than the claims of the '493 patent in several respects. They are not limited to compositions in tablet form. The nonionic hydrophilic surfactant does not have to be selected from poloxamers. There is a wider range of claimed proportions between the nonionic hydrophilic surfactant and the active. While these differences are not necessarily major, even relatively nuanced variations in claim language between patent generations have barred importing disclaimers to a child claim. *See, e.g.*, *Res.QNet.com*, 346 F.3d at 1382 (declining to import disclaimer to child claim because the claim language "each of a plurality of fields" differed from "each field" and emphasizing that "[a]lthough the related patents are similar, their claims are not identical.").

While these differences are likely enough to render improper the importation of the disclaimer from the parent patent, the differences in claim language between the '493 and '800 patents do not end there. Most significantly, claim 1 of the '800 patent does not contain the explicit claim limitation requiring that the pharmaceutical composition as a whole not contain a polysorbate surfactant. Because the disclaimer in the '493 patent was created by explicit claim language that does not appear in the '800 patent, rather than arguments about the meaning of common claim language, Federal Circuit precedent compels the Court to conclude that the disclaimer should not carry forward to the '800 patent. *See Regents*, 717 F.3d at 943; *Ventana*, 473 F.3d at 1182; *Invitrogen Corp.*, 429 F.3d at 1078; *ResQ.Net.com*, 346 F.3d at 1383. The Federal Circuit's requirement that prosecution history address a limitation in common with the

[8] Defendants correctly point out that claim 3 of the '493 patent limits the benzofuran derivative to dronedarone hydrochloride, more closely mirroring the '800 patent.

child patent in order to be relevant "is not a mere technicality: it is necessary to support the inference that the patentee's earlier arguments are also applicable to the claim limitations of the patent-in-suit." *Regents*, 717 F.3d at 944.

During prosecution of the '493 patent, the applicant did not argue that specific claim language should be given a narrower construction based on the specification. The applicant instead added an affirmative claim limitation to independent claim 1 of the '493 patent that expressly excluded polysorbate surfactants from the entire pharmaceutical composition. Accordingly, the disclaimer with regard to the '493 patent was not based on any claim term later appearing in the '800 patent. By not including that explicit language of exclusion in the claims of the '800 patent, the applicant was therefore not seeking to "recaptur[e] *through claim interpretation* specific meanings disclaimed during prosecution," the prevention of which is the principal purpose of the doctrine of prosecution history disclaimer. *Omega Eng'g.*, 334 F.3d at 1323 (emphasis added). Instead, the applicant deliberately chose to write different, broader claims—which the applicant was entitled to do—by, among other changes, not including the express claim language excluding polysorbate surfactants. The Federal Circuit has consistently rejected the application of prosecution history disclaimer in similar circumstances, explaining that:

> [Defendant] provides no plausible reason why the prosecution histories of either [of] the [parent] patents are relevant to the construction of claim 3 of the '233 patent. Notably, there are no common claim terms in dispute. *Indeed, the present case involves the absence of a claim term. The patentee's whole point in filing the application that resulted in the '233 patent was to secure broader claims.*

Advanced Cardiovascular Sys., Inc. v. Medtronic, Inc., 265 F.3d 1294, 1305–06 (Fed. Cir. 2001) (emphasis added); *see also Saunders*, 492 F.3d at 1333 (holding that disclaimer from parent did not carry over to child patent where "all the claims in the [parent] patent explicitly require at least one pressure activated seal while the [child] patent omits that language from the asserted

claims"); *Ventana*, 473 F.3d at 1182 (rejecting carryover of disclaimer when it was based on "claim language that expressly required reagent in the reagent container to be 'dispensable directly to a sample,'" but the claims of the child parent did not contain such limiting language); *Warner Chilcott Co. v. Amneal Pharm., LLC*, 2014 WL 1391536, at *7 (D.N.J. Apr. 9, 2014) (holding that disclaimer did not carry over where, in the child patent, "the patentee changed more than a modifier, omitting a claim limitation entirely . . . and using different language to claim more precise scope . . . ."). Accordingly, Defendants here are essentially asking the Court to add an entire limitation to claim 1 of the '800 patent based on the file history of the '493 patent. To do so would be improper. *See Regents*, 717 F.3d at 945 ("'Although statements in a file history may of course be used to explain and potentially limit the meaning of claim limitations,' they 'cannot be used to add an entirely new limitation to the claim.'" (quoting *Serrano v. Telular Corp.*, 111 F.3d 1578, 1584 (Fed. Cir. 1997)).

Also relevant to the analysis is that the prosecution history of the '800 patent demonstrates that the examiner was not under the impression that nonionic hydrophilic surfactants did not include polysorbates. *See Ventana*, 473 F.3d at 1183 (emphasizing statements by the examiner showing that the examiner did not consider the claim term to be limited by the prosecution history). Specifically, the examiner based several early rejections of claims in the '800 patent on the disclosure of polysorbate surfactants in the prior art, demonstrating the examiner's awareness that the patentee intended its claims to encompass polysorbate surfactants. (D.I. 87-1 at 71; D.I. 87-2 at 53). The applicant did not argue in response to these rejections that the claims did not encompass polysorbate surfactants, but instead distinguished Martin-Algarra on the grounds that it disclosed a solution rather than a solid composition and contemplated amiodarone rather than dronedarone. (D.I. 87-3 at 33). Together, these pieces of the prosecution

history leave little doubt that the applicant sought to include polysorbates within the claims of the '800 patent and the examiner knew this was the case. *See Ventana*, 473 F.3d at 1183 (finding it significant that "the inventors did not rely on [the previously disclaimed feature] as a distinction between the claims at issue in [the] case and the prior art").

Lastly, I find Defendants' reliance on *Hakim v. Cannon Avent Grp. PLC*, 479 F.3d 1313 (Fed. Cir. 2007) and *Heuft Systemtechnik GMBH v. Indus. Dynamics Co.*, 282 F. App'x 836 (Fed. Cir. 2008) to be unpersuasive. In *Heuft*, throughout the prosecution of the parent patent, the applicant "not only repeatedly distinguished its claims over [a prior art] reference on the basis of the large exit angle's ability to stably arrange the containers, it also amended all of those claims to require an exit angle between 30° to 100°, a span which directly tracks the only discussion in the specification indicating an appropriate range for stably arranging containers." *Heuft*, 282 F. App'x at 840–41. The patentee also attempted to amend the specification and argued that "[t]he critical features [of the invention] are the distance between the railings 14 and *above all the angle B at which that distance narrows down in the third area 28*." *Id.* at 840 (alterations in original). Here, by contrast, the claim limitation that eventually disclaimed polysorbates in the parent '493 patent was at odds with the specification, which expressly contemplated polysorbates as examples of nonionic hydrophilic surfactants. (*See, e.g.*, '493 patent, col. 2, ll. 45–46, 59–60 ("The nonionic hydrophilic surfactant used in the composition of the invention can be chosen from . . . ethoxylated polysorbates, such as polysorbate 20, polysorbate 40, polysorbate 60, and polysorbate 80 . . . .")). Moreover, the applicant here certainly did not rely on the lack of polysorbates as a key feature of the invention throughout prosecution. It merely added that claim limitation after several rejections by the examiner. Likewise, in *Hakim*, the applicant filed a continuation application replacing the word slit with the

word opening, despite emphasizing throughout prosecution of the parent patent that the slit distinguished the claimed invention over prior art that disclosed an opening. *See Hakim*, 479 F.3d at 1316. The examiner allowed the continuation claims without further prosecution and the Federal Circuit merely held, "The district court did not err in holding that the examiner's action in allowing the continuation claims without further prosecution was based on the prosecution argument in the parent." *Id.* at 1317. Here, by contrast, the applicant never emphasized during prosecution that the absence of polysorbates distinguished the '493 patent from the prior art. The extensive prosecution history of the '800 patent also demonstrates the examiner's awareness that the applicant intended to capture polysorbates within the claims and therefore satisfies the concern raised in *Hakim* that, without additional prosecution, the claims may have been allowed based on the prosecution history of the parent patent.

Accordingly, I conclude that the wholesale disclaimer of polysorbate surfactants from the pharmaceutical composition, which appears in the claims of the '493 patent, should not carry over to the '800 patent.

IV. CONCLUSION

For the foregoing reasons, the Court finds that: (1) Defendants' proposed product labels induce infringement of claims 1–4, 6, 8–13, and 16 of the '167 patent; (2) Defendants' proposed product labels do not induce infringement of claim 5 of the '167 patent; (3) there are substantial non-infringing uses for dronedarone and therefore there is no contributory infringement; (4) all of the asserted claims of the '167 patent are valid; and (5) the disclaimer of polysorbate surfactants in the '493 patent does not carry over to the '800 patent.

Sanofi is directed to submit an agreed-upon form of final judgment within two weeks.